ETS: RESPIRATORY DISEASES AND CONDITIONS IN NONSMOKING ADULTS AND CHILDREN

VOLUME III

9/93

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THIS ISSUE BINDER IS INTENDED TO PROVIDE A BASIC, COMPREHENSIVE REVIEW OF THE SCIENTIFIC LITERATURE REGARDING A SPECIFIC TOPIC ON ETS AND THE HEALTH OF NONSMOKERS.

PRIMARY STUDIES AND REVIEWS HAVE BEEN HIGHLIGHTED TO IDENTIFY (1) USEFUL OR HELPFUL INFORMATION (YELLOW HIGHLIGHT) AND (2) ADVERSE RESULTS OR OPINIONS (BLUE HIGHLIGHT).

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INTRODUCTION
ETS AND CHILDHOOD AND ADULT RESPIRATORY DISEASE/SYMPTOMS

This issue binder is designed to provide a comprehensive review of the major literature on environmental tobacco smoke and childhood and adult respiratory disease/symptoms. The book has been divided into subsections: (A) childhood respiratory disease/symptoms; (B) childhood pulmonary function; (C) compromised children such as asthmatics and children with cystic fibrosis; (D) otitis media; (E) adult respiratory disease/symptoms; (F) adult pulmonary function; (G) compromised adults; and (H) confounders.

Each section provides a short introduction to the topic. Major studies are preceded by a short abstract and followed by published critiques of the study. Each of the studies is highlighted to facilitate understanding of the issue: 1) favorable points are highlighted in yellow, and 2) unfavorable points are highlighted in blue. Tables and charts in the notebook are also highlighted in yellow (favorable) and blue (unfavorable).

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PARENTAL SMOKING AND COMPROMISED CHILDREN

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PARENTAL SMOKING AND CHILDHOOD ASTHMA

The data on parental smoking and its possible association with asthma in children are inconclusive. While several studies report an association between asthma and parental smoking,[1-18] others do not.[19-26] The epidemiologic studies are inconsistent in several aspects, including the data collection method, the definition of asthma, and the method of estimating exposure to parental smoking.

The majority of the epidemiological studies of parental smoking and childhood asthma utilize questionnaires to estimate a child's exposure to ETS. However, there are several studies (most of which are fairly recent) that measure cotinine levels in bodily fluids to estimate a child's exposure. These studies report a statistically significant association between parental smoking and asthma in children. However, there are several problems with the use of cotinine levels to estimate ETS exposure. While some reports may suggest that cotinine is a reliable marker for <u>total</u> exposure to ETS, many others do not for a variety of reasons.[27-36] For example, it has been reported that individuals metabolize nicotine in different ways at different times and that elimination rates for cotinine vary among individuals. In addition, recent research indicates that diet may contribute to levels of nicotine and cotinine found in the body, thereby interfering with reported exposure levels from nicotine in ambient air.[37] Scientists have

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also noted that different methods of analysis may influence final recorded levels of cotinine.[38] Finally, it has been observed that because nicotine is largely present in the gas-phase of ETS, measurement levels of its metabolite, cotinine, do not reflect exposures to other constituents present, for example, in the particulate phase of ETS.[29]

There is at least one group of researchers that has performed clinical studies of the possible association between exposure to ETS and exacerbation of asthma in children. In 1990, German researchers Oldigs et al., reported that exposing children with bronchial asthma to cigarette smoke sufficient to reach a level of 20 parts per million (ppm) carbon monoxide for one hour did not affect their lung function or bronchial responsiveness.[23] These authors have reported similar data in subsequent studies.[25]

Other authors, utilizing questionnaires to estimate exposure, have reported similar findings. In 1990, Charles Sherman and his co-investigators reported that neither paternal nor maternal smoking "bore an apparent relation to the development of asthma" in a sample of children, aged 5 to 9, enrolled in public and parochial schools in East Boston, Massachusetts in 1974.[24]

In 1992, Martinez et al. reported that childhood asthma was associated with maternal smoking in children whose mothers had 12 or fewer years of education.[39] However, they reported that there

was no association between maternal smoking and asthma in children of mothers with more than 12 years of education. While not suggested by the authors of this study, these data could be interpreted as providing support for the theory that socioeconomic differences are important confounders in studies of parental smoking and childhood asthma.

A British researcher, Strachan, has implicated damp housing as a potential factor in the development of childhood asthma.[40] After controlling for the possible influence of housing tenure, number of people per room, number of smokers in the household, and gas cooking, he reported that the relationship between damp housing and childhood asthma in his study population remained "highly significant."

Another group of authors, Horwood et al., reported that parental smoking habits were not significantly associated with the development of asthma in a birth cohort of New Zealand children.[21] The authors concluded that "asthma in early childhood appeared to be inherited to some extent, its age of expression was related to the child's sex, and it had a complex interaction with other forms of allergic disease."

In another study of New Zealand children, Mitchell et al. reported that the following factors appeared to be precipitating factors for asthma attacks: 1) weather (70%); 2) infection (61%);

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3) stress or excitement (25%); 4) dust (24%); 5) pollen (17%); 6) food (13%): 7) running out of medicines (11%); 8) animals (10%); and 9) exercise (4%).[41] A "miscellaneous agents" category, including passive smoking, noncompliance, etc., were reported to be associated with the precipitation of asthma attacks in only 4 percent of patients.

In summary, there are many potential confounding variables which should be controlled for in any study which purports to show a relationship between parental smoking and childhood asthma. In an article which argues against parental smoking, the author concedes, "the relative risk or odds ratio in the larger studies which controlled to some degree for confounding has been modest, of the order of 1.5" and that confounding "is a consideration wherever the measure of effect is modest."[42]

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CHILDHOOD ASTHMA: COTININE STUDIES

WILLERS ET AL. 1991	RR = 2.6	(95% CI: 1.2-5.3)
EHRLICH ET AL. 1992	RR = 2.0	(95% CI: 1.1-3.4)
CHILMONCZYK ET AL. 1993	RR = 1.7	(95% CI: 1.4-2.1)

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CHILDHOOD ASTHMA: ACUTE EXPOSURE STUDIES

OLDIGS ET AL. 1990	11 CHILDREN	ONE HOUR OF EXPOSURE TO PASSIVE CIGARETTE SMOKE WAS NOT ASSOCIATED WITH AIRWAY OBSTRUCTION OR CHANGES IN BRONCHIAL RESPONSIVENESS IN CHILDREN WITH MILD ASTHMA
OLDIGS ET AL. 1991	11 CHILDREN	ONE HOUR OF EXPOSURE TO PASSIVE CIGARETTE SMOKE WAS NOT ASSOCIATED WITH CONSISTENT CHANGES IN LUNG FUNCTION OR BRONCHIAL RESPONSIVENESS IN CHILDREN WITH MILD ASTHMA
MAGNUSSEN 1993	11 CHILDREN	ONE HOUR OF EXPOSURE TO PASSIVE CIGARETTE SMOKE WAS NOT ASSOCIATED WITH CONSISTENT CHANGES IN LUNG FUNCTION OR BRONCHIAL RESPONSIVENESS IN CHILDREN WITH MILD ASTHMA

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Leeder, S.R., Corkhill, R.T., Irwig, L.M., Holland, W.W., Colley, J.R.T. "Influence of family factors on asthma and wheezing during the first five years of life" Brit J. prev. soc. Med. 30: 213-218, 1976.

ABSTRACT. Family factors associated with the incidence of asthma and wheezing during childhood have been studied in a cohort of over 2000 children who, together with their families, were followed-up for five years. Episodes of wheezing not regarded by the parents as asthma had a different pattern of association with family factors to that found for asthma. The outcome of the two conditions in terms of ventilatory function at the age of five years was also different, in that children with a history of asthma had a lower peak expiratory flow rate than did children with a history of non-asthmatic wheezing.

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Brit. J. prev. soc. Med. (1976), 30, 213-218

Influence of family factors on asthma and wheezing during the first five years of life

S. R. LEEDER*, R. T. CORKHILL, L. M. IRWIG†, AND W. W. HOLLAND
Department of Community Medicine, St Thomas's Hospital Medical School, St Thomas's Hospital, London
J. R. T. COLLEY
Department of Community Health, Bristol

Leeder, S. R., Corkhill, R. T., Irwig, L. M., Holland, W. W., and Colley, J. R. T. (1976). *British Journal of Preventive and Social Medicine*, 30, 213-218. **Influence of family factors on asthma and wheezing during the first five years of life.** Family factors associated with the incidence of asthma and wheezing during childhood have been studied in a cohort of over 2000 children who, together with their families, were followed-up for five years. Episodes of wheezing not regarded by the parents as asthma had a different pattern of association with family factors to that found for asthma. The outcome of the two conditions in terms of ventilatory function at the age of five years was also different, in that children with a history of asthma had a lower peak expiratory flow rate than did children with a history of non-asthmatic wheezing.

Attacks of wheezing are common events in childhood in the United Kingdom. Two studies showed that some 20% of children received attention from their general practitioner for at least one episode of wheezing during their first decade (Fry, 1961; Goodall, 1958). The relationship between attacks of wheezing accompanying acute lower respiratory infection, sometimes termed wheezy bronchitis, and wheezing precipitated by allergens, emotional stress, or exercise is particularly difficult to define (*British Medical Journal*, 1973; Gordis, 1973). It is likely that in some cases episodes of wheezing mark the beginning of chronic bronchial asthma (Williams and McNicol, 1969; Gandevia *et al.*, 1973). In this paper we report observations on different family factors associated either with episodes of wheezing considered by parents not to be asthma, and with what the parents termed asthma, in over 2000 children who were studied, together with their families, until the children were five years old. We reasoned that if all attacks of wheezing were in reality mild attacks of asthma, they would be associated with the same family factors as frank asthma.

Methods and Materials

The methods and materials pertaining to this study are described in the preceding paper.

Results

By the age of five years, one or more episodes of asthma had been reported in 3·4% of boys and 2·9% of girls. Wheezy, whistling, or chesty episodes without asthma were reported in 22·5% of boys and 20·7% of girls.

Episodes of wheezing rather than asthma were associated with a history of bronchitis or pneumonia in children during their first year of life, 41·2% of children with a history of bronchitis or pneumonia in the first year subsequently suffered from wheezing, compared with 19·2% of children without bronchitis or pneumonia (Table I: relative risk for wheeze is 2·15). Asthma was not so strongly associated with bronchitis or pneumonia in the first year, 4·3% of children with this history suffered from subsequent

*Present address: Department of Medicine, McMaster University Medical Centre, Hamilton, Ontario, Canada L8S 4J9.
†Present address: National Research Institute for Occupational Diseases, P.O. Box 4788, Johannesburg 200, Republic of South Africa.

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TABLE I

INCIDENCE PER 100 INDEX CHILDREN OF WHEEZING* IN FIRST FIVE YEARS OF LIFE BY BRONCHITIS OR PNEUMONIA IN FIRST YEAR, AND BY PARENTAL ASTHMA-WHEEZE

		Parental Asthma-Wheeze			
		Neither	One	Both	Total
Bronchitis or pneumonia in the first year	No	17·7 (1333)	24·2 (421)	16·0 (50)	19·2 (1804)
	Yes	37·7 (138)	46·8 (77)	44·4 (18)	41·2 (233)
	Total	19·6 (1471)	27·7 (498)	23·5 (68)	21·7 (2037)†

Populations in parentheses
*Wheezing excludes children who had asthma.
†Total excludes 96 index children with missing first, third, fourth, and fifth year data and an additional 16 with missing initial data on parent pairs.

asthma, compared with 3·0% of children without this history (Table II: relative risk for asthma is 1·41). In children with one parent with a history of asthma-wheeze, the incidence of asthma was 5·4% compared with 2·5% of children whose parents were both free of asthma-wheeze. The incidence of wheezing was also higher in children with one parent with a history of asthma-wheeze (27·7%) compared with children of parents without such a history (19·6%). However, the risk was no greater, and sometimes less, if both parents had asthma-wheeze. This inconsistent trend may partly be a consequence of some rates being based on small numbers (Tables I and II). There was no consistent relationship between smoking and cough-phlegm in the parents and asthma in the children, although conclusions are limited once more by small numbers of children with asthma in some cells (Table III). By contrast, wheezing was consistently more common in children when their parents smoked or suffered from cough-phlegm (Table IV).

Asthma was reported more commonly in children of parents in the upper social than in children of lower social class parents (Table V). However, the rates were based on small numbers and the social class gradients were not wholly consistent at all ages; for example, the lowest incidence occurred in children up to the age of three years with parents from social class III. Wheezing was more common in children of lower social class parents. Area of residence had no influence on the incidence of asthma or wheezing.

As some of the family factors examined in the preceding tables were themselves interrelated, it was difficult to assess the influence of each individual factor upon the incidence of asthma or wheezing in the index children. To investigate these relationships, two logistic models were fitted to the data, one with the incidence of asthma in the index children as the outcome variable, and the other with the incidence of wheezing as the outcome variable. The independent variables included in both models were parental

TABLE II

INCIDENCE PER 100 INDEX CHILDREN OF ASTHMA* IN FIRST FIVE YEARS OF LIFE BY BRONCHITIS OR PNEUMONIA IN FIRST YEAR, AND BY PARENTAL ASTHMA-WHEEZE

		Parental Asthma-Wheeze			
		Neither	One	Both	Total
Bronchitis or pneumonia in the first year	No	2·3 (1333)	5·5 (421)	2·0 (50)	3·0 (1804)
	Yes	3·6 (138)	5·2 (77)	5·6 (18)	4·3 (233)
	Total	2·5 (1471)	5·4 (498)	2·9 (68)	3·2 (2037)†

Populations in parentheses.
*Asthma includes children who may have wheezed as well.
†Total excludes 96 index children with missing first, third, fourth and fifth year data and an additional 16 with missing initial data on parent pairs.

TABLE III

INCIDENCE PER 100 INDEX CHILDREN OF ASTHMA* IN FIRST FIVE YEARS BY PARENTAL COUGH-PHLEGM AND SMOKING HABITS

Parents Smoking‡	Parental Cough-Phlegm (During Period First to Fifth Year)			
	Neither Parent Ever Positive	Symptom Changed in One or Both Parents	One or Both Parents Always Positive	Total
Neither	2·9 (307)	1·5 (134)	— (4)	2·5 (445)
Habit changed in one or both	3·9 (279)	3·3 (299)	— (27)	3·5 (605)
One parent consistently smoking	3·3 (184)	2·2 (228)	5·8 (52)	3·0 (464)
Both smokers	1·1 (90)	4·0 (249)	8·0 (25)	3·6 (364)
Total	3·1 (860)	3·0 (910)	4·6 (108)	3·1 (1878)†

Populations in parentheses.
*Asthma includes children who may have wheezed as well.
†Total excludes 72 index children with missing third, fourth, and fifth year data and an additional 199 with missing first to fifth year data on parent pairs.
‡Considered over the full five years of the study.

TABLE IV

INCIDENCE PER 100 INDEX CHILDREN OF WHEEZING* IN FIRST FIVE YEARS BY PARENTAL COUGH-PHLEGM AND SMOKING HABITS

Parents Smoking	Parental Cough-Phlegm (During Period First to Fifth Year)			
	Neither Parent Ever Positive	Symptom Changed in One or Both Parents	One or Both Parents Always Positive	Total
Neither	16·6 (307)	27·6 (134)	25·0 (4)	20·0 (445)
Habit changed in one or both	13·3 (279)	26·1 (299)	29·6 (27)	20·3 (605)
One parent consistently smoking	11·4 (184)	28·1 (228)	23·1 (52)	20·9 (464)
Both smokers	21·1 (90)	27·3 (249)	36·0 (25)	26·4 (364)
Total	14·9 (860)	27·1 (910)	27·8 (108)	21·6 (1878)†

Populations in parentheses.
*Wheezing excludes children who had asthma.
†Total excludes 72 index children with missing third, fourth, and fifth year data and an additional 199 with missing first to fifth year data on parent pairs.

TABLE V

INCIDENCE PER 100 INDEX CHILDREN OF ASTHMA OR WHEEZING* DURING FIRST FIVE YEARS BY PARENTAL SOCIAL CLASS AT FIFTH YEAR

Illness in Children of Parents According to Social Class	Age in Years						Population
	By Age Three		By Age Four		By Age Five		
	Asthma	Wheezing	Asthma	Wheezing	Asthma	Wheezing	
Social class I and II	2·0	17·2	3·1	19·2	4·0	20·8	751
III	1·0	20·2	2·1	22·3	2·7	23·5	997
IV and V	1·4	21·2	1·8	24·5	2·5	27·3	278
Unknown	3·9	13·7	3·9	17·7	3·9	17·7	51
Total	1·5	19·1	2·5	21·3	3·2	22·9	2077†

*Asthma includes children who may have wheezed as well; wheezing excludes children who had asthma.
†Total excludes 72 index children with missing third, fourth, and fifth year data.

smoking, parental cough-phelgm, parental asthma-wheeze, number of siblings and their history of bronchitis or pneumonia and of asthma-wheeze, the sex of the index child, history of bronchitis or pneumonia in the first year of life, social class of the father when the child was aged five years, and area of residence.

In asthma, a history of parental asthma-wheeze was the only statistically significant factor. However, with wheezing, parental cough-phlegm and bronchitis or pneumonia during the first year of life of the child were both found to be statistically significant. The model was then refitted with these two factors alone as independent variables. The crude and adjusted incidence rates using this model are presented in Table VI, which shows that bronchitis or pneumonia during the first year of life had the greater effect upon the incidence of wheezing.

The influence of a history of asthma or wheezing on peak expiratory flow rate at five years was examined in those children for whom these data were available (Table VII). Peak expiratory flow rates were adjusted for differences in sitting height at age five years. Children with a history of both asthma and bronchitis or pneumonia had a significantly lower mean peak expiratory flow rate than those with a history of bronchitis or pneumonia alone; a difference of 17·4% ($P < 0{\cdot}001$). Mean peak flow rates in children with a history of wheezing and bronchitis or pneumonia did not differ significantly from those

TABLE VI

CRUDE AND ADJUSTED INCIDENCE RATES PER 100 CHILDREN OF WHEEZING* FOR LEVELS OF EACH FACTOR WITH ESTIMATES OF THEIR EFFECTS

Factor and Level	Crude Incidence Rate	Adjusted Incidence Rate	Significance of the Factor in the Model		
			χ^2	df	P
Parental cough-phlegm					
Neither	17·7 (1263)	17·6	22·69	2	< 0·0005
One	27·2 (670)	26·3			
Both	34·6 (78)	30·3			
Bronchitis or pneumonia in the first year					
No	18·9 (1781)	18·8	43·63	1	< 0·0005
Yes	41·3 (230)	39·4			
Total	21·5 (2011)†	—	—	—	—

Populations in parentheses.
*Wheezing excludes children who had asthma.
†Total excludes 96 index children with missing first, third, fourth, and fifth year data and an additional 42 with missing initial or first year data on parent pairs.

TABLE VII

MEAN PEAK EXPIRATORY FLOW RATES IN CHILDREN AGED FIVE YEARS, BY HISTORY OF ASTHMA, WHEEZING, BRONCHITIS, OR PNEUMONIA

Symptom Group	Mean PEFR‡	Population	Standard Error of the Mean	Significance of Difference Between Means of Groups With and Without Symptoms	
				t	P
Nil	151·5	292	1·5		
Asthma without bronchitis or pneumonia	—	3	—		
Wheezing without bronchitis or pneumonia	149·2	40	4·1	0·51	0·6< P <0·7
Asthma with bronchitis or pneumonia	118·6	10	8·2	3·95	P <0·001
Wheezing with bronchitis or pneumonia	140·3	33	4·5	2·34	0·01< P <0·02
Bronchitis or pneumonia only	143·5	76	3·0	2·38	0·01< P <0·02
Total	—	454†	—	—	—

*Asthma includes children who may have wheezed as well; wheezing excludes children who had asthma.
†Total excludes 4 index children with successful flow rate measurements at age five years but with missing first to fourth year data. The remaining 1691 children were not measured at age five years.
‡Litres/min, adjusted for sitting height at age five years.

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with a history of bronchitis or pneumonia alone. The 40 children with a history of wheezing alone had peak flow rates similar to those of children without a history of asthma, wheezing, bronchitis, or pneumonia.

Discussion

Episodes of wheezing, 'whistling' or 'chestiness' not termed asthma by parents occurred much more commonly (in 21·7% of children) than asthma (3·2%) by the age of five years. Wheezing episodes were closely associated with bronchitis and pneumonia occurring during the first year. Wheezing was also associated with parental cough-phlegm and smoking as was bronchitis or pneumonia in the first year (Leeder *et al.*, 1976). This suggests that at least some of the environmental factors associated with bronchitis or pneumonia may also be important in the development of wheezing episodes in later childhood. Alternatively, genetic factors associated with bronchitis or pneumonia in the first year may also predispose to wheezing in later childhood. Damage to airways caused by bronchitis or pneumonia in early childhood may also make children more liable to wheeze subsequently.

While episodes of asthma in the first five years of life also showed an association with parental history of asthma-wheeze (as did episodes of wheezing not termed asthma) there is little relationship between asthma in the first five years and other family, social, or environmental factors.

In this study, the parents' account of asthma and wheezing in their children was used to define these illnesses. Despite the uncertainties implicit in using parentally reported data, asthma and wheezing were, as discussed, associated with different family factors. Also, the effects of asthma and wheezing on peak expiratory flow rates at the age of five years were different. Children with a history of asthma had lower peak expiratory flow rates at the age of five than the children with a history of wheezing alone. In asthma adequate treatment can often reverse much of the airways obstruction. The low peak expiratory flow rate at the age of five we found in children with a history of asthma may indicate the need for vigorous bronchodilator therapy. Alternatively, this deficit may reflect irreversible airways obstruction (Cade and Pain, 1973). More concerted treatment in the first five years of life may have prevented its development. Whatever the potential for the reversal of the decreased peak expiratory flow rate found in children with a history of asthma, it appears that the parents' account differentiated between important and unimportant illness, according to whether they termed it asthma or wheezing.

The incidence rates for asthma and wheezing obtained in studies of children clearly depend upon how these two conditions are defined and the populations in which surveys are conducted. In a study of Kent schoolchildren, using similar methods to those used in this study, Hamman, Halil, and Holland (1975), found comparable rates of asthma by the age of 11 years to those that we found by the age of five years. Similar incidence rates for asthma were found in a study of schoolchildren in Birmingham (Smith, 1961).

Asthma was reported more commonly in children of upper class parents, whereas the reverse was true of wheezing. These social class trends could reflect differences in reporting behaviour among parents of different social classes. More parents in social classes I and II may report asthma rather than wheezing episodes when confronted with essentially the same illness in their children. Alternatively, there could be a real difference in the social class distribution of asthma. Hamman *et al.* (1975) found a similar trend to the one described in this paper while Dawson *et al.* (1969) in a study in Aberdeen, Scotland, found a social class trend in asthma incidence contrary to ours.

The incidence of wheezing may prove to be more modifiable than that of asthma by changing environmental factors, as attacks of wheezing were closely associated with bronchitis and pneumonia during the first year of life. Bronchitis and pneumonia in the first year have, in turn, been shown to be associated with such factors as parental smoking habits (Colley, Holland, and Corkhill, 1974). Thus, efforts to prevent bronchitis and pneumonia during the first year of life may also reduce the incidence of wheezing and of other chest illnesses in later childhood.

The syndromes of lower respiratory illness in childhood remain poorly defined and it is clear that the precision of diagnosis of these illnesses requires improvement before more effective treatment can be given to the children who require it. On the basis of the epidemiological evidence presented here, it seems most unlikely that all forms of the more frequent lower respiratory illness in childhood are simply manifestations of a single common disorder. There may well be common features in aetiology and natural history between conditions such as asthma and bronchitis, but this is not a good reason to use these terms interchangeably. This is especially important when strategies for prevention of one or other condition are being considered.

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Requests for reprints: R. T. Corkhill, Lecturer in Medical Statistics, Department of Community Medicine, St Thomas's Hospital Medical School, London SE1 7EH.

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ABSTRACT. Data from two random population surveys are used to assess the relationship between parental smoking and the prevalence of asthma in children aged 0-17. Data from a 1977 Midwestern urbanized county indicate that, if mothers smoked, the prevalence of parent reported asthma increased from 5.0 per cent to 7.7 per cent (estimated relative risk of 1.5) and the prevalence of functionally impairing asthma increased from 1.1 per cent to 2.2 per cent (relative risk of 2.0). In a more rural Eastern county in 1980, a lower overall prevalence of asthma was noted. However, similar estimated relative risks of asthma (1.8) and functionally impairing asthma (2.4) were found to be associated with maternal smoking. Inconsistent relationships were found between the estimated prevalence of asthma and paternal smoking. When multivariate controls were introduced, the relationships between maternal smoking and asthma persisted. Estimated attributable risks indicate that between 18 per cent and 34 per cent of the asthma reported in these samples can be attributed to maternal smoking. Implications of these findings for primary care physicians are discussed.

Parental Smoking and the Risk of Childhood Asthma

STEVEN L. GORTMAKER, PHD, DEBORAH KLEIN WALKER, EDD,
FRANCINE H. JACOBS, EDD, AND HOLLY RUCH-ROSS, AB

Abstract: Data from two random population surveys are used to assess the relationship between parental smoking and the prevalence of asthma in children aged 0–17. Data from a 1977 Midwestern urbanized county indicate that, if mothers smoked, the prevalence of parent reported asthma increased from 5.0 per cent to 7.7 per cent (estimated relative risk of 1.5), and the prevalence of functionally impairing asthma increased from 1.1 per cent to 2.2 per cent (relative risk of 2.0). In a more rural Eastern county in 1980, a lower overall prevalence of asthma was noted. However, similar estimated relative risks of asthma (1.8) and functionally impairing asthma (2.4) were found to be associated with maternal smoking. Inconsistent relationships were found between the estimated prevalence of asthma and paternal smoking. When multivariate controls were introduced, the relationships between maternal smoking and asthma persisted. Estimated attributable risks indicate that between 18 per cent and 34 per cent of the asthma reported in these samples can be attributed to maternal smoking. Implications of these findings for primary care physicians are discussed. (*Am J Public Health* 1982; 72:574–579.)

Introduction

The health hazards of cigarette smoking have been well documented and widely accepted.[1-3] Recently attention has focused on the relationship between exposure to cigarette smoke and the health of nonsmokers. Several studies[4-7] have noted the substantial effects of cigarette smoke on "indoor pollution." Repace and Lowrey, for example, conclude that "levels of respirable suspended particulates in places where tobacco is smoked greatly exceed levels found in smoke-free environments, outdoors, and vehicles on busy commuter highways."[8] White and Froeb found that nonsmokers who were chronically exposed to cigarette smoke in the workplace had levels of pulmonary function similar to that of light smokers and lower than nonsmokers in a smoke-free environment.[9] Hirayama found a significantly increased risk of lung cancer for nonsmoking wives of heavy smokers.[10]

The present study focuses upon parental smoking and childhood asthma. Asthma is one of the leading causes of chronic illness in children; children with asthma experience a characteristic hyperreactivity of the airways to a variety of environmental factors, including irritants such as tobacco smoke.[11] Studies have noted relationships between air pollution and the onset of asthma attacks,[12,13] but no significant relationships between parental smoking and the prevalence of asthma have been reported. Several studies have noted relationships between parental smoking and acute respiratory illness in children,[14-18] and the results have been fairly consistent.[19] A significant dose-response relationship was found between parental smoking and reported bronchitis and pneumonia in infants by Harlap and Davies[19] and Colley, *et al.*[20] One study found a dose-response relationship between parental smoking and adenoidectomy and tonsillectomy in children,[21] and another demonstrated a significant relationship to pulmonary function in children.[22] O'Connell and Logan examined clinical records of asthmatic and nonasthmatic children; they found only a small difference in the incidence of parental smoking, but a majority of the parents of their asthmatic children reported that cigarette smoke aggravated the asthma, and elimination of smoking generally led to improvement.[23]

The analyses described below report on the results of two population surveys carried out in 1977 and 1980 in two locations across the United States.

Materials and Methods

A random household health survey was conducted in Genesee County, Michigan in 1977. Information upon 3,072 children (aged 0–17) and their households was obtained from an adult family member, usually the mother. The response rate was 81 per cent. The city of Flint, Michigan (population 165,000 in 1977) is an industrial city in the southeastern region of the state of Michigan. Flint and the surrounding Genesee County (total population 450,000) are heavily dependent upon automobile-related industries for employment.

Berkshire County, Massachusetts (population in 1980 of 146,000) is a relatively rural county which forms the western

From the Departments of Behavioral Sciences, and Maternal and Child Health and Aging, Harvard School of Public Health. Address reprint requests to Steven L. Gortmaker, PhD, Department of Behavioral Sciences, Harvard School of Public Health, 677 Huntington Avenue, Boston, MA 02115. This paper, submitted to the Journal July 27, 1981, was revised and accepted for publication November 18, 1981.

boundary of the State of Massachusetts. The largest city is Pittsfield (1980 population of 53,000). A randomly dialed telephone survey of households with children (aged 0–17) was conducted in 1980, using many identical questions from the Genesee County survey. The response rate for this survey was 81 per cent; information upon 894 children was available for analysis.

The smoking habits of mothers and fathers in the households were assessed using identical questions in both the Michigan and Massachusetts surveys; the respondent was asked whether or not each household member smoked cigarettes, and if so, how much. For analysis, mothers and fathers were classified as either smokers or nonsmokers. The samples were too small to reliably estimate relations involving different amounts of smoking.*

The presence of asthma among children was assessed using a 22-item chronic condition checklist in the Genesee County survey, and a 21-item checklist in the Berkshire County survey. In Genesee County, the parents were handed a card listing all of the conditions (Appendix A). The same checklist except for the item "bronchitis," was read to respondents in the Berkshire County survey. The questions asking about asthma, hayfever, and any other kind of allergy were exactly the same as questions asked in earlier surveys in Rochester, New York[24] and in the National Health Examination Survey,[25] and are very similar to checklists used in the National Health Interview Survey.[26]

If the parent (usually the mother) confirmed that the child had a certain condition, they were asked, "Does it affect his/her ability to attend school or do any of the things a child his/her age usually does?" "Yes" responses to this question were coded as indicating a functionally impairing condition. Parents were also asked whether a doctor had been seen about this condition.

A number of studies have indicated that parent reports in general overestimate the prevalence of clinically diagnosed chronic conditions. Others have noted, however, that overreporting tends to decline with the reported severity of the condition, i.e., more severe conditions, which have a greater impact upon the individual, tend to be more completely reported.[24-27]

For example, a household survey in Alamance County, North Carolina resulted in an estimated prevalence of a variety of respiratory conditions in children under age 21 of 16.3 per cent. In contrast, a clinically validated estimate (moderate and severe cases only) of 2.9 per cent was obtained.[28] Another household survey in Rochester, New York (utilizing exactly the same questions as the present study) produced a prevalence estimate of 3.2 per cent of asthma in children 0–17 years of age. Follow-up interviews of children aged 6–17 resulted in a validated estimate of .9 per cent prevalence of asthma.[24] These estimates are also consistent with validated estimates obtained in a population study on the Isle of Wight in England for 10–12 year olds; a prevalence of asthma of 2.3 per cent was estimated; when only chronically handicapping asthma was considered, this estimate was halved.[29]

In summary, significant errors in the reporting of childhood asthma have been found in studies utilizing parent interviews, although there is evidence that these errors tend to decrease if the severity of the condition is taken into account. It is important to note, however, that these errors will not bias relationships estimated between parental smoking and asthma unless asthma misreporting is related to parental smoking.** Tests for such systematic bias are reported below.

Results

Overall, the estimated prevalence of asthma in these samples appears similar to that found in a national sample of children in the 1963–1965 National Health Examination Survey,[25] 5.3 per cent among children aged 6–11. The corresponding estimates in Genesee County (1977) and Berkshire County (1980) are 6.5 per cent and 2.6 per cent respectively. The lower estimate for Berkshire County also corresponds to relationships reported from National Health Interview Survey data in 1970, which noted a decreased prevalence of asthma among children living in rural areas, as opposed to urban areas.[26]

The estimated prevalence of functionally impairing asthma in the present samples (1.5 per cent, .8 per cent) is also comparable to the clinically validated prevalence estimates noted above; again, a higher prevalence is found in the urban sample.

Validation of these parent reports is made possible through use of other questions in the household surveys. In the Michigan survey, if a child was noted as having asthma, parents were asked if they had "been to a doctor about this?" All of the parents who reported a child with asthma said they had been to a doctor about the child's condition. In the Massachusetts survey, another question asked for all children was the following: "Today or yesterday has (child's name) taken or used any medicine, salves, or pills that were prescribed by a doctor?" Of the 29 children in this sample reported by parents as asthmatic, seven were reported to be taking asthma medication regularly; the medication was specified in six of these cases, and no children without asthma were reported as receiving asthma medication. Of the seven children in the sample identified as having functionally impairing asthma, four were reported to be taking medication for the condition. The answers to both of these survey questions suggest that the parent reports are valid

*Of the mothers who smoked, 61 per cent in the Michigan sample and 56 per cent in the Massachusetts sample reported smoking a half to one pack per day.

**In regression analysis, it is well known that random error in the dependent variable will not bias estimates of regression coefficients, although the explained variance will decrease.[30] The analogous corollary for the logistic regressions used later is derived from the well-known fact that odds ratios that characterize a cross-classification are invariant to multiplication of rows or columns by a constant.[31] Thus, if both smoking and nonsmoking mothers overreport asthma by a proportionate amount, estimates of odds ratios will not be affected.

TABLE 1—Estimated Prevalence of Asthma in Children, by Smoking of Mothers; Genesee County, Michigan (1977) and Berkshire County, Massachusetts (1980).

Site Condition	Maternal Yes	Smoking No	Estimated Relative Risk	χ^2	p-value (one-tailed)
Genesee County, MI (N)	(1,255)*	(1,817)			
Asthma	7.7	5.0	1.53	8.1	.001
Functionally Impairing Asthma	2.2	1.1	1.95	5.4	.01
Berkshire County, MA (N)	(330)	(564)			
Asthma	4.5	2.5	1.83	2.8	.05
Functionally Impairing Asthma	1.2	0.5	2.28	1.2	.13

*Sample sizes are given in parentheses

and again indicate that parent reporting likely increases in accuracy as the severity of the condition increases.

In the Genesee County, Michigan sample, 41 per cent of the children aged 0–17 had mothers who smoked. [redacted]

Data from the more rural Berkshire County sample produced similar estimates of relative risk, although the significance levels were lower due to the smaller sample size. Thirty-seven per cent of the children aged 0–17 in this sample had a mother who smoked. [redacted]

No significant differences in the relationships between maternal smoking and asthma, and maternal smoking and functionally impairing asthma were found between the two geographic areas. Log-linear models were fitted, testing for this three-way interaction, and no significant differences emerged. Thus, data from the two sites were pooled, using a variant of the Mantel-Haenszel procedure.[7] [redacted]

Other Explanatory Variables

The relationship of paternal smoking to childhood asthma was also explored in both samples, but the results were inconsistent. In Genesee County, Michigan, significant relationships were found between paternal smoking and the prevalence of childhood asthma but not of functionally impairing asthma. In Berkshire County, no significant relationships between paternal smoking and the risk of asthma or functionally impairing asthma were observed.

Parents who smoke could conceivably be over-sensitized to the effects of their smoking, and thus could overreport conditions in their children. This possible bias in symptom reporting was explored by looking at the relationship between maternal and paternal smoking and other chronic conditions‡ for which respiratory symptoms might appear. No significant relationships were found.

Multivariate logistic regressions‡‡ were estimated which predicted asthma and functionally impairing asthma among children from mothers' smoking habits, as well as from the smoking habits of fathers, whether the child had hayfever or any other allergies, and socioeconomic and demographic characteristics of the family and child. The coefficient estimates from these equations estimated from

***All tests of the smoking-asthma relationship will be one-tailed tests; other tests will be two-tailed. It should also be noted that the sample in fact consists of data upon clusters of children; thus, even though households were selected randomly, some design effect is introduced into the sample. We estimate from the present samples that roh,[11] the intraclass correlation coefficient which measures this tendency towards homogeneity within clusters, is .16 for asthma, and .21 for function impairing asthma. The effect of this clustering is to reduce the precision of the survey estimates. For example, in the Genesee County sample a 95 per cent confidence interval around the proportion of children reported as asthmatic by mothers that do not smoke can be estimated at 4–6 per cent if the effects of clustering are ignored. If this design effect is taken into account, the 95 per cent confidence interval becomes 3.8–6.2 per cent. Others have found that design effects are less pronounced for regression coefficients than for estimates of means and proportions.[16] Regressions were run based upon households which predicted the proportion of children in a household with asthma, controlling for family size and other variables noted later. These results were consistent with results presented later, and thus indicate no significant consequences of this design effect.

‡These conditions included hayfever and any other allergies.

‡‡These logistic regressions estimate linear associations between the predictor variables and the logarithm of the odds for asthma. They were estimated using MMLA, a computer program which produces maximum likelihood estimates, written by W. W. Hauck, Illinois Cancer Council, Chicago, Illinois.

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TABLE 2—Coefficient Estimates from Logistic Regressions Predicting Asthma and Functionally Impairing Asthma in Children 0–17, Genesee County, MI, 1977

Variable	Equation Predicting Asthma: Coefficient Estimate	t-Statistic	Odds-ratio	Equation Predicting Function-Impairing Asthma: Coefficient Estimate	t-Statistic	Odds-ratio
Mother Smokes (Yes = 1)†	.401	2.45**	1.49	.613	1.94*	1.85
Father Smokes (Yes = 1)	.398	2.40*	1.49	.076	.24	1.08
Age of Child (1 ≤ 5)	−.358	−1.79	.70	−.299	−.78	.74
Sex of Child (1 = male)	.115	.73	1.12	−.236	−.79	.79
Income of Family (1 = poverty; 2 = near poverty; 3 = higher)	.028	.20	1.03	−.077	−.33	.93
Mother's Education	−.226	−2.32*	.80	−.488	−2.44*	.61
Child has Allergies (Yes = 1)	1.169	6.44**	3.22	1.230	3.70**	3.42
Child has Hayfever (Yes = 1)	1.686	8.51**	5.40	1.585	4.36**	4.88

*significant at p = .05
**significant at p = .01
†Other responses coded as "0" if first category is "1"

the Genesee County data are displayed in Table 2 above. A variety of other variables are not included in this Table because they did not add any explanatory power to these equations. These include the number of persons in the household, race, environmental deficiencies observed near the home (available only in the Genesee County sample), number of rooms in the house, and mother's work status.

The most important result of this analysis is that the addition of all of these control variables did not substantially alter the estimated relationships [illegible] and the prevalence of asthma and functionally [illegible] asthma. The estimated odds-ratios which describe these relationships, controlling for the variables, are only attenuated slightly from "unadjusted" estimated odds ratios derived from Table 1.‡‡‡ For example, the odds-ratio relating asthma and maternal smoking changes from 1.57 to 1.49; the corresponding change for the functionally impairing asthma odds ratio is from 1.98 to 1.85. Similar equations were estimated for the Berkshire County sample, resulting in similar estimates of the relationship between maternal smoking and asthma. The smaller sample size from this site, however, resulted in lower levels of statistical significance. These analyses also confirmed the fact that paternal smoking did not in general predict chronic respiratory problems once maternal smoking was controlled.

Bronchitis was included as one of the items on the chronic condition checklist in the Genesee County sample and significant relationships were found between the prevalence of bronchitis and maternal smoking (p < .00[illegible] estimated relative risk of 1.5). However, no association with functionally impairing bronchitis was observed, and no significant association between bronchitis and paternal smoking was found. These relationships suggest another effect of maternal smoking, similar to the known effects of individual smoking upon the production of bronchitis in the smoker.[14] This relationship may also reflect the fact that some children with asthma are misdiagnosed as having chronic bronchitis.[16] The converse, however, could also be true. We reestimated the equations described in Table 2 including an additional control variable indicating whether the child had bronchitis or not. While the bronchitis variable was significant in these equations, maternal smoking was still significantly related to both asthma and function impairing asthma and the coefficient estimates were only slightly attenuated (to 1.42 and [illegible]).

One other variable which could have important implications is the presence of asthma in parents, but we believe that this variable could have an attenuating effect upon the present relationships. We assume that parents with a history of asthma have a smaller probability of taking up smoking. Thus, there could be a selection of "non-asthmatic" parents into the group of smokers, and subsequently a selection of "non-asthmatic" children to smoking parents, a situation that would result in an attenuated relationship between parental smoking and childhood asthma.

Estimates of Attributable Risk

The significance of these estimated relationships for both medical practice and public health are strongly conditioned by the proportion of mothers that smoke; because more than one-third of mothers in both of these samples smoke, the estimated attributable risks* associated with maternal smoking are substantial.[17] The estimates of relative risk in Table 1 indicate that 18 per cent and 23 per cent respectively of asthma in children in the two sites may be

‡‡‡In the present situation, the odds ratio closely approximates the estimated relative risk.

*Attributable risk can be defined as the "maximum proportion of a disease that can be attributed to a characteristic or etiological factor."[17]

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attributed to maternal smoking, and 28 per cent and 34 per cent respectively of functionally impairing asthma in the two populations can be attributed to maternal smoking.

We have already indicated above that the estimated relative risks associated with maternal smoking are somewhat attenuated as control variables are introduced into the logistic regressions: if these estimates are used in the calculations, slightly smaller attributable risks result (e.g., 17 per cent and 26 per cent rather than 18 per cent and 28 per cent).

Because of the small numbers of conditions reported, the 95 per cent confidence intervals[39] around these estimates are necessarily large: for example, the confidence interval around the estimated percentage of asthma in Genesee County, Michigan, attributable to maternal smoking ranges from 5 per cent to 29 per cent. In spite of this imprecision, the similarity of the estimated attributable risks in the two different populations tends to validate the estimates. Other validations are still needed, however, ideally using more refined measures of both the presence of asthma, the level of functional impairment involved, and the actual air pollution which may be attributed to maternal and paternal smoking.

Smoking and Disability Days

Because other studies have reported relationships between acute illness and parental smoking[16-19] and substantial relationships are reported here between asthma and maternal smoking, an obvious question to be addressed is the extent to which the relationships between acute illness and maternal smoking may be due in part or in whole to the relationships estimated here between chronic illnesses such as asthma and bronchitis and maternal smoking. Maternal smoking and the presence of asthma and bronchitis in the Genesee County sample were all associated with the likelihood of a disability day in the past two weeks. When the presence of asthma and bronchitis was controlled, maternal smoking was still significantly ($p < .05$) related to the odds of a disability day, although the magnitude of the estimated relationships was reduced; e.g., the estimated odds ratio changed from 1.46 to 1.29 when these controls were introduced. Thus, it appears that the relationships estimated above between maternal smoking and the prevalence of chronic respiratory conditions do not account for all of the often reported relationships between parental smoking and acute respiratory illnesses in children.

Discussion

It is useful to conceptually distinguish three possible roles by which an exogenous factor like tobacco smoke might play a role in the pathogenesis of asthma. Such a factor

> "... might be responsible for the inception of asthma by inducing a state of hyperreactivity in the bronchi. Second, it might maintain and reinforce hyperreactivity. Third, it might provoke the expression of hyperreactivity, giving rise to clinically recognizable attacks of asthma."[40]

While the present data do not shed light on the precise role of maternal smoking in the development of childhood asthma, the analyses clearly indicate an influence controlling for other known factors such as hayfever and allergies.[41] Although estimates of attributable risk should be interpreted with these comments in mind, the present data suggest that maternal smoking can be considered an important factor in the occurrence of childhood asthma.

These data can also be considered as another illustration of the extent to which indoor air pollution is a significant determinant of individual health status. As current energy conservation measures in the United States reduce the flow of air through households, the consequences of indoor pollution due to cigarette smoking could certainly increase in magnitude.

The findings from this study suggest that an opportunity exists for health care providers to help prevent asthma in children, and to reduce the level of functional impairment of asthmatic children. One strategy would be to encourage smoking mothers of children with clinically diagnosed asthma to quit smoking. Some effective therapies have been devised to help smokers end their habit,[39] and referrals to such programs could be arranged.

A number of current pediatric texts do not mention such an approach to treating the asthmatic child.[11,36] Evaluations of the possible efficacy of these interventions in reducing the prevalence of asthma and functionally impairing asthma could add significantly to current knowledge.

A broader preventive strategy could involve encouraging the reduction or elimination of maternal smoking among families with a history of allergies. Such families have a greater risk of producing allergic children. This approach parallels the commonly accepted practice of avoidance therapy with household pets for allergic families.[40] There are also substantial benefits to be gained by the mothers themselves if these interventions are successful.

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APPENDIX A

Checklist of Chronic Conditions and Impairments:

(a) Asthma
(b) Hay Fever
(c) Any other kind of allergy
(d) Any trouble with his/her kidneys
(e) Anything wrong with his/her heart
(f) Any difficulty hearing
(g) Any difficulty seeing (even with glasses)
(h) Trouble speaking (stammering, lisping, hard to understand)
(i) Missing fingers, hand, arm, toes, foot or leg
(j) Any permanent stiffness or deformity of foot, leg, fingers, arm or back
(k) Condition present since birth, such as club foot or cleft palate
(l) Paralysis of any kind
(m) Mental impairment or retardation
(n) Arthritis
(o) Bronchitis
(p) Epilepsy, convulsions
(q) Cerebral palsy
(r) Diabetes
(s) Anything else

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Fergusson, D.M., Horwood, L.J. "Parental Smoking and Respiratory Illness During Early Childhood: A Six-year Longitudinal Study" Pediatr Pulmonol 1(2): 99-106, 1985.

SUMMARY: The relationship between parental smoking habits and lower respiratory illness and symptoms during the first 6 years of life was studied in a birth cohort of New Zealand children. This showed that maternal (but not paternal) smoking was associated with significant increase in rates of lower respiratory infection and lower respiratory symptoms during the child's first 2 years. This association persisted when a range of perinatal, social and familial factors were taken into account statistically. After two years there was no detectable association between parental smoking habits and lower respiratory infection. Further, there was no evidence to suggest that children whose parents smoked had increased risks of asthma or rates of asthmatic attacks during early childhood.

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Parental Smoking and Respiratory Illness During Early Childhood:

A Six-year Longitudinal Study

D. M. Fergusson,* BA Hons, and L. J. Horwood, BA, BSc

Summary. The relationship between parental smoking habits and lower respiratory illness and symptoms during the first 6 years of life was studied in a birth cohort of New Zealand children. This showed that maternal (but not paternal) smoking was associated with significant increase in rates of lower respiratory infection and lower respiratory symptoms during the child's first 2 years. This association persisted when a range of perinatal, social, and familial factors were taken into account statistically. After two years there was no detectable association between parental smoking habits and lower respiratory infection. Further, there was no evidence to suggest that children whose parents smoked had increased risks of asthma or rates of asthmatic attacks during early childhood. (Key words: asthma, children, cigarette smoking, lower respiratory illness, parental smoking.) *Pediatr Pulmonol 1985; 1:99–106*

A number of studies have examined the relationship between parental smoking and lower respiratory illness in children and, in general, the results have suggested that parental smoking may be harmful to children. Perhaps the best-documented findings relate to the increased rates of lower respiratory infection and symptoms that have been observed in children under 2 years of age whose parents (and, particularly, the mothers) smoke. This association has been found in a variety of studies that have used both retrospective and concurrent measures of medical consultation for lower respiratory infection, maternal reports of lower respiratory symptoms, and hospital attendance data. The correlation has been shown to persist when a large number of potentially confounding factors have been controlled, including family social background, family composition, lower respiratory illness in the child's family, infant feeding practices, and perinatal history. In at least two studies the association in children between early lower respiratory illness and parental smoking has been shown to disappear at around 2 years of age.

A further series of studies have suggested that, in school-aged children, parental smoking and, particularly, maternal smoking is associated with increased rates of lower respiratory symptoms, lower respiratory infection, and reduced pulmonary function. The introduction of control factors, including measures of family social background and the children's smoking habits, has not appreciably altered these correlations. At the same time, not all studies of school-aged populations have found linkages between parental smoking and pulmonary function.

A number of investigators have also examined the relationship between parental smoking and the onset and frequency of asthma during childhood, and the majority of studies have failed to find any tendency for the children of parents who smoke to be more prone to asthma than those of nonsmokers. An exception to this trend, however, was reported by Gortmaker et al., who found a small but statistically significant tendency for children whose parents smoked to suffer greater rates of asthma.

Although the general conclusion that may be drawn from this literature is that smoking is harmful for children, some aspects of the findings suggest that this relationship may not be a simple one. In particular, the emerging evidence tends to suggest that the effects of parental smoking vary with the age of the child (being most marked during early childhood), the source of the parental smoke (with maternal smoking having a greater influence than paternal smoking), and the disease that is studied (with lower respiratory infection and symptoms being more influenced by parental smoking habits than childhood asthma).

To place these issues in perspective, this pa-

From the Christchurch Child Development Study, Department of Paediatrics, Christchurch Clinical School of Medicine, Christchurch Public Hospital, Christchurch, New Zealand.

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Address correspondence and reprint requests to Dr. Fergusson

per reports the results of a six-year longitudinal study of the relationship between parental smoking habits and lower respiratory illness in children in a sample of New Zealand children. The aims of the paper are: 1) To examine the relationship between rates of lower respiratory infection or symptoms in children, parental smoking habits, and the children's ages and to devise a statistical model describing the linkages between these variables. 2) To examine the association between parental smoking and the onset of asthma and the frequency of asthmatic attacks during early childhood.

Method

The data were collected during the first eight stages of the Christchurch Child Development Study. A birth cohort of children born in the Christchurch (New Zealand) urban region in mid-1977 was studied at birth, 4 months, and annual intervals to the age of 6 years using a combination of a home-based interview with the mother supplemented by information from hospital records, general practitioner notes, and other documentary sources. The general methods of data collection and the quality control of the data have been described in previous papers.[illegible] The following information was used in the present analysis.

Medical Consultation for Lower Respiratory Infection. Information on medical consultations for bronchitis, bronchiolitis, and pneumonia was collected for each child for each year of life. This information was gathered from several sources including maternal recall, diaries of the children's health that were kept each year by the mothers, and information from general practitioner records.

Maternal Reports of Lower Respiratory Symptoms. Mothers were questioned about whether their child had had a "chesty cold" or "wheezy chest" at each year of life irrespective of whether a medical consultation had been involved. Separate items for chesty cold and wheeze were used for children up to 2 years of age. However, during the first year of the study, our interviewers reported that many mothers had difficulty distinguishing between wheeze and general chestiness. To overcome this possible ambiguity, from the second year onward we used a single item that covered both chesty cold and wheeze. The measure used in this analysis is based on whether at each year of life, the mother reported that her child had suffered from chesty colds or wheeze irrespective of whether medical attention was sought for these conditions.

Asthma During Early Childhood. To measure whether a child was prone to asthma and, if so, the frequency of the asthmatic attacks, four measures were developed.

1.—whether the child had ever attended a medical practitioner for the treatment of wheeze that had been diagnosed as asthma or wheezy bronchitis. (Wheezy bronchitis was included in the definition of asthma on the basis of Williams and McNicol's[illegible] conclusion that the two conditions are indistinguishable; however, only 8% of all diagnoses were for wheezy bronchitis.)

2.—whether the mother had ever reported that her child had suffered an asthmatic attack irrespective of whether this attack had been treated medically.

3.—the frequency of medical attendance from birth to 6 years for episodes of wheeze that were diagnosed as asthma or wheezy bronchitis.

4.—the frequency of maternal reports of asthmatic episodes during the period from birth to 6 years irrespective of whether medical attendance was sought.

The first two measures defined the proportion of children who, according to medical diagnosis or maternal belief, were prone to asthma; the second two measures described the frequency of asthmatic attack among those children who were susceptible to asthma.

Parental Smoking. At each year, mothers were questioned about their daily cigarette intake and the intake of the child's father.

Control Factors

To take account of the possibility that any apparent correlations between parental smoking and lower respiratory illness could have arisen from the effects of common confounding variables, the following measures were used for the purpose of statistical control.

Perinatal Status. Measures of the children's birthweights and estimated gestational ages were obtained from hospital records.

Family Composition and Social Background. As part of the routine data collected during the course of the study, information was available on maternal ages, family sizes, maternal educational levels, the children's ethnicity, and family socioeconomic statuses as measured by the Elley and Irving[illegible] scale of socioeconomic status for New Zealand.

Family Atopy. At the initial interviews with

Table 1—Risks per 100 Children of Medical Consultations for Bronchitis/Pneumonia and Maternal Reports of Lower Respiratory Symptoms by Age of Child and Parental Smoking Habits (Number of Children in Sample in Parentheses)

	Medical Consultation for Bronchitis/Pneumonia				Maternal Reports of Lower Respiratory Symptoms			
	Maternal smoking (cigs/day)				Maternal smoking (cigs/day)			
	0	1-10	11+	Total	0	1-10	11+	Total
Children 0-2 years								
Paternal smoking (cigs/day)								
0	14.6 (575)	22.7 (75)	25.2 (115)	17.0 (765)	60.9 (575)	66.7 (75)	70.4 (115)	62.9 (765)
1-10	9.1 (66)	14.0 (43)	23.5 (17)	12.7 (126)	54.6 (66)	74.4 (43)	70.6 (17)	63.5 (126)
11+	18.3 (120)	25.0 (52)	28.4 (81)	22.9 (253)	67.5 (120)	63.5 (52)	71.6 (81)	70.0 (253)
Total	14.7 (761)	21.2 (170)	26.3 (213)	17.8 (1144)	61.4 (761)	67.7 (170)	70.9 (213)	64.1 (1144)
Children 2-4 years								
Paternal smoking (cigs/day)								
0	13.7 (590)	9.9 (71)	17.0 (112)	13.8 (773)	53.2 (590)	59.2 (71)	58.9 (112)	54.6 (773)
1-10	16.0 (75)	8.7 (23)	20.8 (24)	15.6 (122)	60.0 (75)	34.8 (23)	58.3 (24)	54.9 (122)
11+	15.2 (105)	13.9 (36)	15.6 (64)	15.1 (205)	59.4 (105)	52.8 (36)	62.5 (64)	55.6 (205)
Total	14.2 (770)	10.8 (130)	17.0 (200)	14.3 (1100)	53.8 (770)	53.1 (130)	60.0 (200)	54.8 (1100)
Children 4-6 years								
Paternal smoking (cigs/day)								
0	11.1 (586)	17.5 (59)	10.7 (121)	11.5 (766)	51.5 (586)	55.9 (59)	53.7 (121)	52.2 (766)
1-10	6.1 (66)	17.4 (23)	13.0 (23)	9.8 (112)	51.5 (66)	60.9 (23)	70.0 (23)	57.1 (112)
11+	12.3 (106)	12.5 (40)	7.8 (77)	10.8 (223)	59.8 (106)	52.5 (40)	54.6 (77)	53.4 (223)
Total	10.8 (758)	15.5 (122)	10.0 (221)	11.2 (1101)	51.7 (758)	55.7 (122)	55.7 (221)	53.0 (1101)

the children's mothers. Information was collected on the presence (both past and present) of asthma, allergic rhinitis, and eczema in the mother, biological father, and siblings.

Breastfeeding History. From information collected from hospital notes and maternal interviews, estimates of the duration of time (if at all) the child was breastfed were obtained.

Pets in the Home. At each year, mothers were questioned about the presence of pet cats or dogs in the children's families, and an estimate of the extent of exposure to these animals was created for each child by summing the number of years the pets had been in the child's family.

Family Life Events. From two years onward, mothers were questioned about the occurrence of adverse or stressful life events using a 2?-item check list based on an abbreviated version of the Holmes and Rahe[11] social readjustment rating scale. For each year, an estimate of the extent of exposure to stressful life events was created by summing the number of such events reported.

Sample Sizes

The initial cohort comprised 1,265 children, but as a result of emigration from New Zealand and losses to follow up, this cohort was reduced in 6 years to 1,115 children. This reduced sample represented 88% of the original cohort and 95% of those cohort members still alive and resident in New Zealand. However, throughout the analysis, sample sizes varied with the age of the children because complete data on parental smoking and respiratory illness for the full six-year period were not available for every child. (These were children who had left New Zealand, and who re-entered the study on their return.) The variations in sample size are reflected in tables 1, 4, and 5.

Results

Medical Consultation for Lower Respiratory Infection and Maternal Reports of Lower Respiratory Symptoms. Table 1 shows the associations between parental smoking habits and rates

Table 2—Rates per 100 Children Aged 0-2 years of Bronchitis/Pneumonia and Lower Respiratory Symptoms by Maternal Smoking Adjusted for Family Size, Perinatal Status, Breastfeeding, and Family Social Circumstances

Maternal Daily Cigarette Intake	Bronchitis/Pneumonia	Lower Respiratory Symptoms
Nonsmoker	15.3	61.6
1-10 per day	19.5	65.0
11+ per day	24.5	68.2

of medical consultation for bronchitis and pneumonia and maternal reports of lower respiratory symptoms in their child during the period from birth to 6 years. (The data are presented in two-year blocks for simplicity, but a parallel analysis of the year-by-year trends in the data produced similar results.) [redacted] However, after the children reached 2 years of age, there appeared to be little or not association between parental smoking habits and the rates of lower respiratory illness or symptoms. These conclusions were confirmed by fitting a series of hierarchical log linear models[16] to the data on rates of lower respiratory illness shown in the table. This procedure led to the following conclusions. [redacted] Paternal smoking did not make a contribution to the variability in rates of illness when considered alone or in combination with maternal smoking. 2) After the children reached 2 years of age, there were no significant associations between parental smoking habits and rates of lower respiratory illness or symptoms.

The results in table 1 do not take into account the possible effects of other social or familiar factors that may be correlated with maternal smoking habits and childhood lower respiratory illness or symptoms. To examine this issue, the data for the first 2 years were reanalyzed using logistic regression methods[17] in which maternal smoking together with the measures of family social background, family composition, infant feeding practices, and perinatal history were related to rates of medical consultation for bronchitis and pneumonia and rates of maternal reports of symptoms. Results of this analysis clearly showed that, even when all control factors were taken into account, there was a significant association during the children's first two years between maternal smoking habits and rates of lower respiratory infection ($P < 0.01$) and a marginally significant ($P = 0.06$) association between maternal smoking habits and rates of lower respiratory symptoms. From the fitted model, estimates were obtained using the methods described by Lee[18] of the association between maternal smoking and rates of lower respiratory infection and symptoms that were adjusted for the effects of the control factors. [redacted] children under the age [redacted].

Our initial analyses examined the data in a series of cross-sectional two-year blocks. To analyze the dynamic relationships that existed between maternal smoking and rates of lower respiratory illness and symptoms throughout the child's first 6 years, the data was used to form a 3 × 2 contingency table,* which described the associations between maternal smoking during the child's first 2 years and rates of lower respiratory infections and symptoms throughout the child's first 6 years. This table was fitted using log linear modeling methods. A summary of the analysis is shown in table 3, which gives values

Table 3—Fitted Log Linear Model of Maternal Smoking, Medical Consultations for Lower Respiratory Illness, and Maternal Reports of Lower Respiratory Symptoms (0-6 yrs)

Factor		χ^2	df	P
First order effects				
Maternal smoking	(A)	687.68	183	$P < 0.0001$
Medical consultations (0-2 yrs)	(B)			
Symptoms (0-2 yrs)	(C)			
Medical consultations (2-4 yrs)	(D)			
Symptoms (2-4 yrs)	(E)			
Medical consultations (4-6 yrs)	(F)			
Symptoms (4-6 yrs)	(G)			
Second order effects				
AB		15.4[illegible]	2	$P < 0.01$
AC		7.96	2	$P < 0.05$
BC		176.75	1	$P < 0.0001$
BD		[illegible]	1	$P < 0.001$
CE		[illegible]	1	[illegible]
DE		139.40	1	$P < 0.0001$
DF		96.28	1	$P < 0.001$
EG		[illegible]	1	$P < 0.001$
FG		[illegible]	1	$P < 0.0001$
Residual		[illegible]	[illegible]	[illegible]

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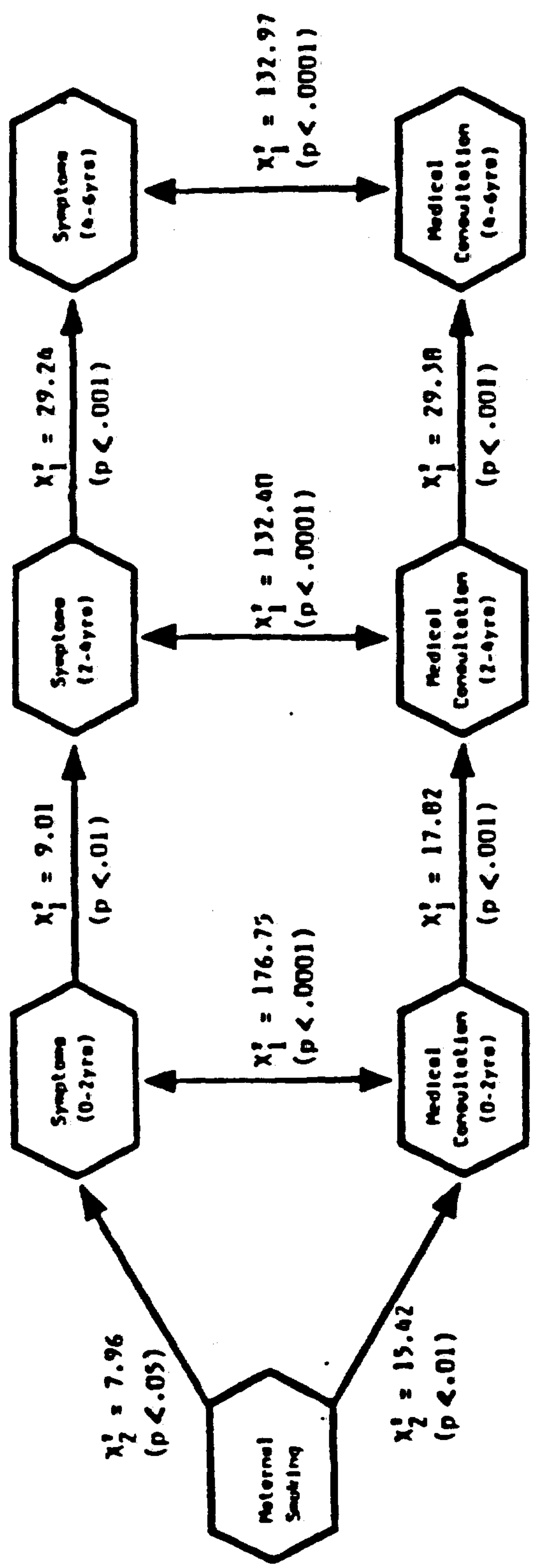

of the log likelihood ratio chi-square statistics for the various effects in the fitted model. The results can be readily interpreted from figure 1, which shows the fitted model using the conventions described by Freeman and Jekel.[31] In this diagram, variables that were significantly related are shown linked by solid lines and the size of the association is indicated by the log likelihood ratio chi square value and its corresponding level of significance. Variables that were not significantly related are not linked by lines. The following conclusions can be drawn from the figure. 1) Maternal smoking was associated with [redacted] the children's first 2 years. 2) Within each measuring period there were very strong associations ($P < 0.0001$) between medical consultations for lower respiratory illness and maternal reports of lower respiratory symptoms. These associations arose because if the child had attended a medical practitioner for lower respiratory illness, his or her mother almost invariably reported lower respiratory symptoms. 3) There were significant associations ($P < 0.001$) between rates of medical consultation for lower respiratory illness across measurement periods. [redacted] respiratory infection during the period from [redacted] to 6 years. A similar causal-chain model links the measures of maternal reports of lower respiratory symptoms.

As may be seen from Table 3, the model depicted in figure 1 produced a very satisfactory fit to the observed data ($\chi^2 = 131.73$; df = 172, $P = 0.99$).

Asthma During Early Childhood. Table 4 compares the number of children having at least one asthmatic episode (defined both on the basis of medical consultation and maternal report) by the age of 6 years with parental smoking habits. Inspection of the table shows no clear tendency for the proportions of asthmatic children to vary with parental smoking habits, and this was confirmed by log linear modeling of the results, which indicated that there was no significant association between being asthmatic and parental smoking habits.

Figure 1—Fitted log linear model of maternal smoking, medical consultation for lower respiratory illness, and maternal reports of lower respiratory symptoms in children 0–6 years of age.

Table 4—Risks Per 100 Children of Having at Least One Asthmatic Episode by the Age of 6 Years by Parental Smoking Habits (Number of Children in Sample in Parentheses)

	Medical Consultation				Maternal Report			
	Maternal Smoking (cigs/day)				Maternal Smoking (cigs/day)			
	0	1-10	11+	Total	0	1-10	11+	Total
Paternal smoking (cigs/day)								
0	12.6	9.0	6.8	11.4	13.5	10.5	8.1	12.5
	(460)	(67)	(74)	(601)	(460)	(67)	(74)	(601)
1-10	15.1	17.2	16.9	16.3	15.1	17.2	16.9	16.3
	(86)	(64)	(65)	(215)	(86)	(64)	(65)	(215)
11+	17.2	12.3	9.1	13.4	17.2	14.0	10.6	14.4
	(93)	(57)	(66)	(216)	(93)	(57)	(66)	(216)
Total	13.6	12.8	10.7	13.0	14.2	13.8	11.7	13.7
	(639)	(188)	(205)	(1,032)	(639)	(188)	(205)	(1,032)

[redacted] This issue is examined in table 5, which shows the frequency of asthmatic attacks per 100 children (measured both on the basis of maternal report and frequency of medical consultation) related to parental smoking habits. While there was substantial variability in the rates of asthmatic attacks depending on the combinations of parental smoking, there was no clear trend in the results that would suggest increased parental smoking was associated with increases in the rate of asthmatic attacks. This impression was confirmed by log linear modeling of the data in table 5, which showed there were no significant associations between parental smoking and the frequency of asthmatic attacks.

To examine the possible effects of various confounding factors on the associations between parental smoking and the occurrence of asthma in children and the rates of asthmatic attacks, the data were further analyzed using regression methods in which a number of control factors, including gender, family history of asthma, early eczema, early respiratory infection, breastfeeding history, pets in the family, family life events, and family social background were introduced as factors in stepwise analyses. The analysis of the risk data in table 4 was conducted using multiple logistic regression, whereas the frequency of attack data (table 5) were analyzed using multiple linear regression methods based on the square root of the number of episodes of asthma occurring during the period from 0–6 years. All analyses indicated that there were no significant relationships between parental smoking habits and risks of childhood asthma or rates of asthmatic attacks even when the set of control factors was taken into account statistically.

Discussion

The findings of this six-year longitudinal study indicate that the effects of parental smoking on childhood respiratory illness depended on the child's age, the source of parental smoke, and the outcome studied. [redacted] However, after this time, maternal smoking did not make a significant contribution to the rates of medical consultation or reports of lower respiratory symptoms. Paternal smoking was not related to lower respiratory illness at any time, and neither paternal nor maternal smoking was related to the risk of asthma or the frequency of asthmatic attacks during the child's first 6 years. [redacted] However, the mechanisms involved are as yet unclear. Colley et al.[7] proposed a genetic explanation in which parental smoking is related to a genetic disposition to lower respiratory illness, which is reflected in higher rates of morbidity among the offspring of smokers. However, this explanation seems highly unlikely given that, according to most studies, maternal smoking is more important in this regard than is paternal smoking, which would suggest a mode of inheritance in which a predisposition to lower respiratory illness is sex linked to the child's mother! Fergusson et al.[8] have suggested

Table 5—Rate Per 100 Children Aged 0–6 Years of Asthmatic Attacks by Parental Smoking (Number of Children in Sample in Parentheses)

	Medical Consultation				Maternal Report			
	Maternal smoking (cig/day)				Maternal smoking (cig/day)			
	0	1-10	11+	Total	0	1-10	11+	Total
Paternal smoking (cig/day)								
0	57.4	69.3	56.8	56.4	124.6	79.1	10[illegible].4	116.6
	(460)	(67)	(74)	(601)	(460)	(67)	(74)	(601)
1-10	76.7	34.4	72.3	69.8	166.3	98.4	20[illegible].5	156.7
	(86)	(64)	(65)	(215)	(86)	(64)	(65)	(215)
11+	95.7	38.6	56.1	68.5	163.4	59.7	130.2	125.9
	(93)	(57)	(66)	(216)	(93)	(57)	(66)	(216)
Total	65.6	41.0	61.5	60.3	135.8	79.8	14[illegible].4	126.9
	(639)	(188)	(205)	(1,032)	(639)	(188)	(205)	(1,032)

a hypothesis in which prolonged exposure to cigarette smoke has an irritant effect that exacerbates the respiratory infections that normally occur during early childhood, making it more likely that lower respiratory symptoms will develop.

However, whereas previous studies[6-10] have reported associations between lower respiratory symptoms, lower respiratory illness or impaired pulmonary function, and parental smoking for school-aged children, we were unable to find any association between parental smoking and respiratory illness or symptoms during the period from 2–6 years. [redacted] Tager et al.[10] argue that such early exposure coupled with increased risks of early lower respiratory illness may cause structural changes that are reflected in increased rates of lower respiratory symptoms and reduced pulmonary function during later childhood. The results of the longitudinal log linear analysis presented in this paper cast some light on the plausibility of this hypothesis. In particular, the model suggested that maternal smoking was associated with an increased risk of lower respiratory illness and symptoms during the child's first 2 years, and that early respiratory illness or symptoms during the first 2 years are associated with subsequent illness or symptoms. At first sight these results would appear to support the hypothesis that early exposure to parental smoke leads to later respiratory illness. However, this view does not take into account the statistical "slippage" that occurs within this system of relationships. Thus, while maternal smoking does influence early respiratory illness, and early respiratory illness is related to later respiratory illness, maternal smoking made a negligible direct or indirect contribution to later respiratory illness for our cohort. This suggests that the tendency for rates of lower respiratory illness or symptoms to be correlated over time cannot be attributed to the common effects of maternal smoking on respiratory function.

A more plausible explanation of the existing data would appear to be that there are two mechanisms involved in the correlations between parental smoking and lower respiratory illness and symptoms in children. [redacted] This effect is relatively short lived and disappears at around the age of 2 years. However, in the light of the findings of Tager et al.[10] there is also evidence to suggest that prolonged exposure to parental smoking may have the effect of gradually compromising the lower respiratory system of children so that around the middle-school years, children become at greater risk of lower respiratory illness and reduced pulmonary function.

In confirmation of three previous studies,[10,11] we were unable to show any correlation between parental smoking and either the onset or frequency of asthmatic attacks during early childhood. [redacted] implicated in the development of asthma or the

frequency of asthmatic attacks in young children. At the same time, Gortmaker et al.[22] were able to show a small but nonetheless significant association between parental smoking habits and asthma in a cross-sectional sample of children aged from 0–17 years. It seems possible that these differences may reflect age differences between samples. [redacted] It should also be noted that the apparent correlation between parental smoking and asthma reported by Gortmaker et al.[22] could be a disguised correlation between asthma and smoking in the child,[30,31] as this factor was not controlled for in their analyses.

[redacted] function. Such relationships can only be clarified by further longitudinal studies that examine the way in which varying exposure times to parental smoking have dynamic effects on both the susceptibility to lower respiratory illness and pulmonary function throughout childhood.

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ABSTRACT. The role of social and familial factors in the development of childhood asthma by age 6 years was studied in a birth cohort of New Zealand children. Rates of asthma varied markedly with the child's sex; boys had twice the rate of asthma as girls. In addition, the factors associated with asthma varied with the child's sex. For boys, wheeze during infancy, early eczema, and parental asthma were all significant risk factors; for girls, the only risk factor was early eczema. Proportional hazards modeling of the data failed to show any significant associations between the development of asthma and a large range of other social and familial factors including breast-feeding, parental smoking habits, pets in the child's family, stress in the family, or family social background. It was concluded that asthma in early childhood appeared to be inherited to some extent, its age of expression was related to the child's sex, and it had a complex interaction with other forms of allergic disease. There was no evidence to suggest that the structure, practices, or dynamics of the child's family played a significant role in the development of asthma for children in this birth cohort.

Social and Familial Factors in the Development of Early Childhood Asthma

L. J. Horwood, BA BSc, D. M. Fergusson, BA Hons, and F. T. Shannon, FRCP, FRACP

From The Christchurch Child Development Study, Department of Paediatrics, Christchurch Clinical School of Medcine, Christchurch Public Hospital, Christchurch, New Zealand

ABSTRACT. The role of social and familial factors in the development of childhood asthma by age 6 years was studied in a birth cohort of New Zealand children. Rates of asthma varied markedly with the child's sex; boys had twice the rate of asthma as girls. In addition, the factors associated with asthma varied with the child's sex. For boys, wheeze during infancy, early eczema, and parental asthma were all significant risk factors; for girls, the only risk factor was early eczema. Proportional hazards modeling of the data failed to show any significant associations between the development of asthma and a large range of other social and familial factors including breast-feeding, parental smoking habits, pets in the child's family, stress in the family, or family social background. It was concluded that asthma in early childhood appeared to be inherited to some extent, its age of expression was related to the child's sex, and it had a complex interaction with other forms of allergic disease. There was no evidence to suggest that the structure, practices, or dynamics of the child's family played a significant role in the development of asthma for children in this birth cohort. *Pediatrics* 1985;75:859–868; *childhood asthma, breast-feeding, smoking, parental asthma.*

There have been a large number of studies of the social and familial factors associated with childhood asthma. Among the factors that have been suggested to lead to increased risks of asthma are: a family history of asthma[1-10] and other atopic conditions[6,10]; a history of other atopic conditions in the child[6,7,11,12]; viral respiratory infections in early childhood[13-16]; the child's sex[4,12,13,17]; psychosocial and family stress factors[18-21]; artificial feeding[9,22-24]; parental smoking[25,26]; the presence of cats and dogs in the home[9,27]; and social background.[12,26,28-31]

However, the conclusions drawn from these studies have been limited by the fact that they have often been conducted upon small samples, from selected clinical populations, using cross-sectional or retrospective case-control designs. There appears to have been no prospective study that has examined the role of social and familial factors in the development of asthma in a large and representative population of children.

This paper reports on the results of a 6-year prospective study of the development of asthma in a birth cohort of New Zealand children. The aims of the study were: (1) to identify the social and familial factors associated with increased risks of asthma in early childhood, and (2) to develop a proportional hazards model to describe the way in which various social and familial factors and combinations of these factors influenced the likelihood of developing asthma.

METHOD

The data were collected during the first 6 years of the Christchurch Child Development Study. In this study, a birth cohort of Christchurch (New Zealand) children has been studied at birth, age 4 months, and at annual intervals to age 6 years. At each stage, information was collected on the child's health, family social background, and other factors by means of a structured interview with the child's mother supplemented by information from hospital records, general practitioner's notes, and diary of medical attendances kept by the mother. The methods of data collection and quality control have been described in detail in previous papers.[7,32-35]

From the data base of the study the following

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variables were selected for analysis: childhood asthma, family history of atopy, child health in the first year, early feeding and home environment, psychosocial factors, and family social background.

Childhood Asthma

This was based on whether the child had made two medical consultations before the age of 6 years for wheeze or associated symptoms that were diagnosed as asthma or wheezy bronchitis. Wheezy bronchitis was included in the definition of asthma on the basis of the conclusions of Williams and McNicol[36] that the two conditions were indistinguishable. (Only 8% of all diagnoses were for wheezy bronchitis.) The criterion of at least two diagnoses was used as there is some uncertainty about the significance of a single diagnosis of asthma in early childhood. The frequency distribution of the number of medical attendances for asthma is given in Table 1, which shows that by age 6 years, 10.3% of cohort members had made two or more attendances. In all cases, the diagnosis of asthma or wheezy bronchitis was made after the child was 1 year old. An analysis of the effects of varying the stringency of the definition of asthma and of excluding diagnoses of wheezy bronchitis is given under "Results." Information on childhood asthma and wheezy bronchitis was obtained from an annual diary of medical attendances kept by the child's mother in 60% of cases. In the remaining 40% of cases, this information was based on maternal recall supplemented by direct contacts with the child's family doctor.[7,35] The majority (94%) of asthmatic attacks were treated by the child's family doctor, but nonetheless 24 of the 109 (22%) children who suffered two or more asthmatic episodes had been admitted to hospital for asthma.

Family History of Atopy

Information on the history of atopic conditions (both past and present) in both of the child's biologic parents and among the child's full siblings was collected prospectively at the initial (birth) interview.[7] From this information, four dichotomous measures were constructed: (1) parental asthma—whether there was a known history of asthma in one or both parents; (2) parental eczema—whether there was a known history of eczema in one or both parents; (3) parental allergic rhinitis—whether there was a known history of allergic rhinitis in one or both parents; and (4) sibling asthma—whether there was a known history of asthma in any of the child's full siblings. For the measures of parental atopy, consideration was given to analyzing both maternal and paternal atopy separately. However, it was found that combined indices based on a history of atopy in either parent were as effective predictors as measures based on data for each parent.

TABLE 1. Frequency Distribution of Number of Medical Consultations for Asthma (Ages 0 to 6 Years)

No. of Consultations	No.	%
0	915	86.6
1	32	3.0
2	26	2.5
3	20	1.9
4	12	1.1
5–9	25	2.4
10–14	13	1.2
15+	13	1.2
Total	1,056	100.0

Child Health in First Year

The following measures were constructed on the basis of maternal reports, diary records, and records of general practitioner and hospital attendances in the first year: (1) eczema—whether the child had at least one medical attendance for skin rash that was diagnosed as eczema[33,34] (Because information on medical attendances for eczema were based on maternal reports supplemented by information from medical records, it was not possible to distinguish reliably between atopic and seborrheic eczema.); (2) wheeze—whether the child had attended a medical practitioner for wheezy chest not diagnosed as asthma, or the mother reported respiratory wheeze that did not require medical attention[37,38]; (3) lower respiratory tract infections—the total number of episodes of bronchitis, bronchiolitis, or pneumonia treated by a medical practitioner[37,38]; and (4) total respiratory infections—the total number of episodes of respiratory tract illness (either upper or lower) treated by a medical practitioner.[37]

Early Feeding and Home Environment

The following measures were used as indicators of the child's early feeding history and home environment:

Infant Milk Diet (Age 0 to 4 Months). This was based on information collected from (1) obstetric unit notes of the child's feeding history shortly after birth, (2) a diary record kept by the mother on the child's feeding history from birth to age 4 months (85% of mothers kept such a diary), and (3) questioning the mother about the child's feeding history to determine whether he or she had ever been given any cow's milk. (A detailed account of methods for assessing the breast-feeding history of this cohort has been published previously.[33–35])

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The early milk feeding history of the sample was classified as follows: (1) children who had been totally bottle fed since birth and never received any breast milk; (2) children who had been breast-fed but who had received some cow's milk before age 4 months; and (3) children whose early milk diet was breast milk only and who had never received cow's milk by age 4 months.

Parental Smoking. Each year, information was collected on the smoking habits of the child's parents. The history of parental smoking over the survey period was classified as follows: (1) neither parent smoked at any time; (2) one parent smoked at some time during the survey period; and (3) both parents smoked at some time during the study period.

Cats/Dogs in the Home. Records included information on whether the family had a pet cat or dog.

Psychosocial Factors

To measure the amount of stress, adversity, and social readjustment experienced by the family during the study period the following three measures were constructed.

Family Life Events to Age 6 Years. Each year from 2 years to 6 years, mothers were interviewed using a modified version of the Holmes and Rahe Social Readjustment Rating Scale.[39] This consisted of 20 items which covered such areas as illness in the family, bereavement, financial problems, and marital disharmony. The characteristics of the scale have been described in detail by Beautrais et al.[32] To measure the amount of adversity faced by the family, a life events score was constructed by summing the total number of life events reported over the study period.

Maternal Depression. At 5 years and 6 years, mothers were interviewed on a modified version of the Levine-Pilowsky Depression Questionnaire.[40,41] The scale consisted of 37 items measuring various symptoms of depression. The characteristics of the scale have been described by Fergusson et al.[42] To measure the mother's general level of depression, a scale score was constructed by summing the total number of depressive symptoms reported by the mother over the 2-year period.

Changes of Residence. Records included information on the number of changes of residence experienced by the child from birth to age 6 years.

Family Social Background

The following measures were used as indicators of the family's social situation: (1) maternal age at the birth of the survey child; (2) maternal education classified as—no formal qualifications, secondary qualifications (NZ School Certificate or University Entrance), or tertiary qualifications (University degree or tertiary technical diploma); (3) child's ethnic status—Maori/Pacific Island *v* European/other; (4) family socioeconomic status—based on the Elley-Irving[43] scale of socioeconomic status for New Zealand, which classifies the population into six classes on the basis of parental occupation; and (5) family size at the child's birth.

Sample Size and Response Rates

The analysis is based on a total of 1,056 children for whom complete data on all the variables in the analysis were available. This number represents 83% of the initial cohort of 1,265 children and 91% of the cohort of children who were still alive and resident in New Zealand at age 6 years. Comparison of the obtained sample with the characteristics of the initial cohort indicated that no significant biases had been introduced as a result of sample attrition.

RESULTS

Risk Factors Associated with Development of Asthma

The association between the proportions of children experiencing two or more episodes of asthma by age 6 years and a series of measures of family and social background is shown in Table 2. The results are shown separately for boys and girls, and each association is tested for statistical significance by the χ^2 test. As shown in Table 2: (1) The rate of asthma was higher among boys than girls: 14.3% of boys had developed asthma by age 6 years in contrast to only 6.3% of girls ($\chi^2 = 18.20$; $df = 1$; $P < .0001$). (2) The factors associated with increased risks of asthma differed markedly between the sexes. For girls, the only significant risk factor was eczema in the first year: girls who had eczema were five times more likely to develop asthma ($P < .0001$). For boys, there was also a significant association between asthma and early eczema ($P < .0001$). However, in contrast to girls, boys were more likely to develop asthma when there was a history of early wheeze ($P < .0001$); when there was a parental history of asthma ($P < .0001$) or allergic rhinitis ($P < .01$); and when other siblings had asthma ($P < .01$). (3) For both sexes there were no apparent associations between rates of asthma and breast-feeding, parental smoking, the presence of cats and dogs, various stresses in the family and family social background.

Because many of the variables in Table 2 were intercorrelated, the results do not indicate the net

TABLE 2. Proportions of Children with Two or More Medical Consultations for Asthma (Ages 0 to 6 Years) by Sex of Child and Familial and Social Factors

Variable	Boys	Girls	Total
Family history of atopy			
Parental asthma			
No asthma	11.2 (48/428)	5.8 (25/433)	8.5 (73/861)
Asthma	26.9 (28/104)	8.8 (8/91)	18.5 (36/195)
Significance	$P < .0001$	NS	$P < .0001$
Parental eczema			
No eczema	12.8 (54/422)	5.8 (23/397)	9.4 (77/819)
Eczema	20.0 (22/110)	7.9 (10/127)	13.5 (32/237)
Significance	NS	NS	NS
Parental allergic rhinitis			
No allergic rhinitis	11.2 (39/347)	5.8 (21/363)	8.5 (60/710)
Allergic rhinitis	20.0 (37/185)	7.5 (12/161)	14.2 (49/346)
Significance	$P < .01$	NS	$P < .01$
Sibling asthma			
No siblings with asthma	12.8 (60/469)	6.2 (30/483)	9.5 (90/952)
Siblings with asthma	25.4 (16/63)	7.3 (3/41)	18.3 (19/104)
Significance	$P < .01$	NS	$P < .01$
Child health in first year			
Eczema			
No eczema	12.1 (59/489)	4.9 (24/488)	8.5 (83/977)
Eczema	39.5 (17/43)	25.0 (9/36)	32.9 (26/79)
Significance	$P < .0001$	$P < .0001$	$P < .0001$
Wheeze			
No wheeze	8.9 (26/293)	6.5 (21/325)	7.6 (47/618)
Wheeze	20.9 (50/239)	6.0 (12/199)	14.2 (62/438)
Significance	$P < .0001$	NS	$P < .001$
Lower respiratory tract infections			
0	13.5 (64/474)	6.2 (30/482)	9.8 (94/956)
At least 1	20.6 (12/58)	7.1 (3/42)	15.0 (15/100)
Significance	NS	NS	NS
Total respiratory tract infections			
0	14.6 (25/171)	7.7 (14/181)	11.1 (39/352)
1–2	11.8 (31/262)	5.2 (13/250)	8.6 (44/512)
3+	20.2 (20/99)	6.5 (6/93)	13.5 (26/192)
Significance	NS	NS	NS
Feeding and home environment factors			
Infant milk diet (0–4 mo)			
Bottle milk only	13.0 (16/123)	7.1 (8/113)	10.2 (24/236)
Breast milk and bottle milk	13.3 (42/315)	5.7 (18/314)	9.5 (60/629)
Breast milk only	19.1 (18/94)	7.2 (7/97)	13.1 (25/191)
Significance	NS	NS	NS
Parental smoking			
Neither parent smoked	14.6 (33/226)	7.4 (17/229)	11.0 (50/455)
One parent smoked	12.0 (21/175)	7.1 (12/169)	9.6 (33/344)
Both parents smoked	16.8 (22/131)	3.2 (4/126)	10.1 (26/257)
Significance	NS	NS	NS
Cats/dogs in home			
No	14.4 (15/104)	11.2 (10/89)	12.9 (25/193)
Yes	14.2 (61/428)	5.3 (23/435)	9.7 (84/863)
Significance	NS	NS	NS
Psychosocial factors			
Family life events (1–6 yr)			
0–4 events	12.7 (10/79)	4.7 (5/107)	8.1 (15/186)
5–9 events	13.5 (29/215)	6.6 (13/197)	10.2 (42/412)
10–14 events	15.5 (23/148)	4.8 (5/104)	11.1 (28/252)
15+ events	15.6 (14/90)	8.6 (10/116)	11.7 (24/206)
Significance	NS	NS	NS
Maternal depression score (5–6 yr)			
0–4 symptoms	11.4 (29/255)	5.3 (13/244)	8.4 (42/499)
5–9 symptoms	16.8 (16/95)	8.2 (9/110)	12.2 (25/205)
10–14 symptoms	22.4 (15/67)	5.3 (3/57)	14.5 (18/124)
15–19 symptoms	18.9 (7/37)	4.8 (2/42)	11.4 (9/79)
20+ symptoms	11.5 (9/78)	8.5 (6/71)	10.1 (15/149)
Significance	NS	NS	NS

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TABLE 2—*Continued*

Variable	Boys	Girls	Total
Changes of residence (0–6 yr)			
0	12.0 (22/183)	6.0 (11/182)	9.0 (33/365)
1–2	16.4 (33/201)	5.2 (10/194)	10.9 (43/395)
3–4	15.1 (13/86)	5.6 (5/89)	10.3 (18/175)
5+	12.9 (8/62)	11.9 (7/59)	12.4 (15/121)
Significance	NS	NS	NS
Family social background			
Maternal age			
<20 yr	19.1 (9/47)	4.3 (2/47)	11.7 (11/94)
20–24 yr	14.5 (25/172)	7.4 (11/148)	11.3 (36/320)
25–29 yr	15.5 (31/200)	7.2 (16/221)	11.2 (47/421)
≥30 yr	9.7 (11/113)	3.7 (4/108)	6.8 (15/221)
Significance	NS	NS	NS
Maternal education			
No formal qualifications	15.5 (42/271)	6.2 (17/273)	10.8 (59/544)
Secondary qualifications	13.3 (22/166)	6.4 (9/140)	10.1 (31/306)
Tertiary qualifications	12.6 (12/95)	6.3 (7/111)	9.2 (19/206)
Significance	NS	NS	NS
Child's ethnic status			
Maori/Pacific Island	18.5 (15/81)	3.0 (2/66)	11.6 (17/147)
European/other	13.5 (61/451)	6.8 (31/458)	10.1 (92/909)
Significance	NS	NS	NS
Socioeconomic status			
Professional, executive	14.9 (15/101)	4.3 (5/116)	9.2 (20/217)
Clerical, technical, skilled	12.8 (36/282)	6.3 (18/284)	9.5 (54/566)
Semiskilled, unskilled, unemployed	16.8 (25/149)	8.1 (10/124)	12.8 (35/273)
Significance	NS	NS	NS
Family size			
1	11.9 (25/210)	6.8 (13/190)	9.5 (38/400)
2	15.4 (28/182)	6.7 (13/195)	10.9 (41/377)
3	15.3 (15/98)	7.1 (7/99)	11.2 (22/197)
4+	19.0 (8/42)	0.0 (0/40)	9.8 (8/82)
Significance	NS	NS	NS
Total	14.3 (76/532)	6.3 (33/524)	10.3 (109/1056)

contributions of each of the factors to the rate of asthma during the 6-year period. We describe below a proportional hazards regression model designed to estimate the net effects of the predictor variables on rates of asthma for boys and girls over the period from ages 1 to 6 years.

Proportional Hazards Model of Development of Asthma

The mathematical basis of the proportional hazards model can be summarized briefly as follows. (For a complete mathematical formulation of the model the reader is referred to Cox[44] or Kalbfleisch and Prentice.[45]) Consider some population or sample observed over a series of time intervals (t) during which some subjects are observed to fail (ie, become asthmatic). The distribution of failures over time defines the survivorship function: $S_t = Pr\ (T \geq t)$, where S_t denotes the survivorship probability (Pr) to time t and T is the time to failure.

Associated with the survival function is the hazard function $\lambda(t)$. The hazard at any time t is defined as the conditional probability of failure at time t, given that failure has not occurred prior to this time. An alternative and intuitively more meaningful description of the hazard is the instantaneous failure rate.

Next, consider the situation in which subjects may be classified according to some series of variables or covariates that are assumed to influence the likelihood of failure. Let these covariates be represented by a vector of values z for each subject. The aim of the proportional hazards model is to describe the way in which the hazard varies over time with the set of covariate values. The model assumes the existence of a base-line group of subjects whose vector of covariate values is arbitrarily set to zero. It is also assumed that the effects of the covariate values are to scale the hazard over time in a way that is proportional to the hazard function for this base-line group. This model is: $\lambda(t;z) = \lambda_0(t)e^{z\beta}$, where $\lambda(t;z)$ denotes the hazard at time t for a group of subjects with covariate vector z, $\lambda_0(t)$

is the hazard at time t for the base-line population with covariate values of 0, and β is a vector of regression-like coefficients. The parameters of the model may be estimated by maximum likelihood techniques, and estimates of the asymptotic standard errors of the coefficients β are available.[45]

To examine the net contributions of the risk factors in Table 2 to variations in rates of asthma, a stepwise proportional hazards model was fitted to the data. In this analysis, the age at which the child first developed asthma was defined as the point at which the first of at least two medical attendances for asthma or wheezy bronchitis occurred. In view of the differences seen in Table 2, separate models were fitted for boys and girls. This analysis showed that when all variables were considered, only three of these (parental asthma, early wheeze, early eczema) were significantly related to the development of asthma in boys. For girls, the only significant risk factor was early eczema. The results of the analysis are summarized in Table 3, which shows the significance of each of the risk factors in the model and the values of the proportional hazards coefficient (e^{β}) for each level of each variable. This coefficient may be interpreted in a way that is analogous to the more familiar notion of relative risk: the increase in the instantaneous risk of asthma that is associated with a particular factor when compared with the risk for the base-line population. Definitions of the base-line populations for boys and girls are given in the footnote to Table 3. For boys, the presence of eczema increased the risk of asthma by 3.45 times over the risk for the base-line group; a parental history of asthma increased the risk by a factor of 2.78; and wheeze in the first year by a factor of 2.39. For girls, the presence of early eczema increased the risk of asthma by a factor of 5.80.

From the results of proportional hazards analysis, estimates were obtained of the risk of experiencing two or more episodes of asthma by the age of 6 years conditional on various combinations of risk factors. The results of this analysis are summarized in Table 4, which shows the estimated cumulative rate of asthma at each age conditional on the number of significant factors that the child had. For boys, three factors—early eczema, early wheeze, and parental asthma—were considered; for girls, the only factor was early eczema. The results show: (1) For boys there was considerable variation in the risk of asthma conditional on the number of significant risk factors that were present. Boys who had all three factors (early eczema, early wheeze, and parental asthma) had a probablity of approximately 80% of developing asthma by age 6 years. In contrast, those with none of these factors had a risk of only 7%. The groups of subjects with one or two of the risk factors had results that lay between these extremes. (2) For girls, variations in prognosis were less marked. However, girls who developed early eczema had rates of asthma that were slightly more than five times higher than girls who did not have early eczema.

TABLE 3. Estimated Proportional Hazards Coefficients for Levels of Significant Factors

Variable	Boys* e^{β}	Significance	Girls* e^{β}	Significance
Child eczema				
No eczema	1	$P < .001$	1	$P < .001$
Eczema	3.45		5.80	
Child wheeze				
No wheeze	1	$P < .001$	...	NS
Wheeze	2.39		...	
Parental asthma				
No asthma	1	$P < .001$	...	NS
Asthma	2.78		...	

* Base-line populations for the two models are: (1) for boys—children with no eczema or wheeze in the first year and without a history of parental asthma; (2) for girls—children with no eczema in the first year.

Sensitivity Analysis

Gregg[4] notes that estimates of the prevalence of asthma depend on the stringency of the criteria used to define the condition. To examine the effects of varying the stringency of the definition of asthma on both the prevalence of asthma and the factors associated with the condition, the results were reanalyzed using a series of definitions of asthma of increasing stringency. These definitions required that the child was classified as asthmatic only after he or she had suffered 3, 4, 5, or 6 episodes of wheeze medically diagnosed as asthma or wheezy bronchitis. The results of this analysis are given in Table 5, which shows for each definition the estimated rate of asthma for boys and girls and the proportional hazards coefficients for each risk factor for each analysis. The table shows: (1) The estimated rate of asthma varied sharply with vary-

TABLE 4. Estimated Cumulative Rates of Asthma (per 100 Children Aged 2 to 6 Years) by Number of Significant Risk Factors

No. of Risk Factors	2 yr	3 yr	4 yr	5 yr	6 yr
Boys					
0	1.5	3.0	4.6	5.8	6.8
1	3.7	7.4	11.1	14.0	16.1
2	10.5	20.2	29.1	35.7	40.1
3	29.6	50.9	66.2	75.1	80.1
Girls					
0	1.1	2.2	3.4	4.4	5.4
1	6.0	12.2	18.0	23.2	27.6

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TABLE 5. Proportional Hazards Coefficients (Significance of Factor) for Models Fitted to Rates of Asthma Based on Definitions of Varying Stringency

	No. of Diagnoses Before Child Was Classified as Asthmatic				
	2	3	4	5	6
Boys					
Variable: early eczema	3.45	4.04	4.36	4.18	5.52
Significance	$P<.001$	$P<.001$	$P<.001$	$P<.001$	$P<.001$
Wheeze	2.39	2.79	2.66	3.89	3.40
Significance	$P<.001$	$P<.001$	$P<.001$	$P<.001$	$P<.001$
Parental asthma	2.78	2.90	3.21	3.21	3.63
Significance	$P<.001$	$P<.001$	$P<.001$	$P<.001$	$P<.001$
Rate of asthma	14.3%	11.3%	8.6%	7.3%	6.0%
Girls					
Variable: early eczema	5.80	5.06	3.99	4.20	—*
Significance	$P<.001$	$P<.01$	$P<.05$	$P<.05$	
Rate of asthma	6.3%	4.4%	3.4%	2.5%	2.3%
Overall rate of asthma	10.3%	7.8%	5.9%	4.8%	4.2%

* The number of subjects with asthma was insufficient to estimate coefficient.

ing definitions of the condition. For the total cohort, the rate to age 6 years was 10.3% if two or more episodes was used as the basis of the classification and reduced to 4.2% if six or more episodes was used as a criterion. (2) For boys, the proportional hazards coefficients for each risk factor show a clear tendency to increase as the definition of asthma becomes more stringent. This result is to be anticipated as one would expect that as the severity of the child's asthma increased, the discriminatory power of the risk factors would increase. However, for girls, there is a decline in the values of the proportional hazards coefficients, suggesting that as the stringency of the definition of asthma increased, there was decreased predictive power. The reasons for this are not entirely clear, but it seems possible that the decline in the proportional hazards coefficients reflects the fact that very few girls suffered a significant number of asthmatic attacks, and it is possible that the small numbers studied may have influenced the stability of the proportional hazards coefficients. (3) In any event, the analysis shows that irrespective of the stringency of the definition of asthma, the same constellation of risk factors emerges as being associated with the condition, and, accordingly, it is unlikely that the conclusions drawn in this study can be ascribed to the way in which asthma was defined.

In addition, there has been some debate as to whether wheezy bronchitis and asthma are distinct conditions. To examine the effects of including or excluding diagnoses of wheezy bronchitis from the definitions of asthma, the results were re-analyzed excluding all diagnoses of wheezy bronchitis. As might be expected from the fact that only 8% of all diagnoses were for wheezy bronchitis, the results did not differ depending on whether wheezy bronchitis was included or excluded from the definition.

DISCUSSION

This longitudinal study suggests that a substantial proportion of children had been determined to be suffering from one or more episodes of asthma or wheezy bronchitis by age 6 years. Depending on the stringency of the criteria used to define the child as asthmatic, the proportion of children classified as asthmatic ranged from 10.3% (for those with two or more episodes) to 4.2% (for those with six or more episodes). Despite the fact that the prevalence and incidence of asthma varied with the stringency of definition of the condition, the risk factors associated with asthma remained invariant.

The most notable aspect of the findings was the way in which the child's sex influenced not only the risk of asthma but also the factors that were associated with the condition. Boys had more than twice the rate of asthma; this finding is in agreement with several other reports.[4,7,12,13,17] In addition, the factors associated with the development of asthma in boys differed from those associated with the development of asthma in girls. For boys, parental asthma, early eczema, and wheeze in the first year were significant risk factors. For girls, the only significant risk factor was early eczema. These trends were reflected in the predictability of the condition: it was possible to identify boys with risks of asthma as high as 80% by age 6 years and as low as 7%; by comparison, the prediction of asthma for girls was modest.

The pervasive influence of the child's sex on both the prevalence and correlates of early asthma could suggest that asthma is a sex-limited or sex-influ-

enced condition. However, the possibility has been considered in a previous report on this cohort and a more likely explanation would seem to be that the condition is sex-expressed, with genetically susceptible boys expressing their asthmatic tendencies at the earlier age than genetically susceptible girls.[7] This hypothesis would also account for the changing sex ratios that have been observed in childhood asthma; the condition is more common in boys in early and middle childhood and equally frequent in both sexes in later childhood.[4,5]

It has been long assumed that asthma is related to some generalized tendency to atopic disease so that conditions such as asthma, eczema, and allergic rhinitis tend to run in families.[46] The findings of this and a previous study[7] suggest that this conclusion is an oversimplification inasmuch as detailed analysis of family resemblance in asthma and eczema for this cohort has suggested the presence of three quite distinct components of "inheritance": (1) an asthma-specific tendency whereby asthma in parents is associated with asthma in the child; (2) an eczema-specific tendency whereby eczema in the parents is associated with eczema in the child; and (3) a generalized atopic tendency for both asthma and eczema to occur together. These findings, coupled with the way in which asthma is influenced by the child's sex, suggest the presence of a complicated and at present poorly understood mode of inheritance which cannot be summarized by the unitary concept of atopy.

Several authors[13-16] have suggested that early viral respiratory infection may predispose children to develop asthma. The findings of our study provide only weak support for this view. Overall, there was no association between the rate of respiratory illness during early life and asthma. However, it is possible that this finding is misleading because it may be that only specific types of viral infection predispose children to develop asthma and accordingly one might not expect to find a strong association between overall rates of respiratory illness and subsequent asthma. Unfortunately, it was not possible in this study to classify respiratory illness on the basis of the source of the infection. The correlation between early wheeze and subsequent asthma might suggest a common source of viral infection which predisposes children to wheeze during early life and to develop subsequent asthma, but at the same time it is also possible that the association may simply reflect the difficulties of diagnosing asthma during infancy and that the children who were described as wheezy were merely manifesting the first stages of later asthma.

It has been held that risks of asthma and other forms of atopy can be reduced by exclusive breast-feeding.[9,22-24,47-50] However, in this and several previous studies of the cohort,[33-35] we have been unable to demonstrate benefits for breast-feeding in the reduction of atopic disease. Moreover, the view that breast-feeding prevents atopy has come under criticism recently with many studies reporting no effect or in some cases increases in atopy among breast-fed children.[33-35,51-54] It is notable that in this study, breast-fed boys had higher rates of asthma than other children, although this difference did not reach statistical significance. Although the role of breast-feeding in the prevention of asthma and other forms of atopy remains controversial, it may be fairly claimed that it is unlikely that infant feeding patterns make a major contribution to variability in the risk of asthma or eczema in the child population. However, as we have noted previously it is possible that highly selected subgroups of children may benefit from breast-feeding.[35]

It has been suggested that cigarette smoking may trigger or exacerbate attacks in patients suffering from asthma,[25] and this has led to the speculation that parental smoking may lead to the development of asthma in children.[9] However, we were unable to find any effect for parental smoking on rates of asthma and this confirms the findings of a previous longitudinal study.[8] On the other hand, Gortmaker et al[26] did find a small but statistically significant tendency for the rate of asthmatic attacks to be higher in families in which parents smoked. [redacted] it is not implicated in the etiology or development of the condition. [redacted] does not appear to be implicated in the development of asthma in early childhood.

It has often been suggested that asthma is a psychosomatic illness triggered or caused by various social or personality factors. Recently, this view has fallen into some disrepute and there have been a large number of criticisms of the theory that asthma is a psychosomatic condition.[18,19] Our study indicates that stress in the family is not related to the development of childhood asthma and this coupled with the contradictory and confused findings on both childhood psychopathology and abnormal parenting among asthmatic children tends to support the conclusions of Werry[19] that there is no good evidence that asthma is necessarily a psychosomatic disease. In a previous study of this cohort,[32]

we have been able to show that a series of conditions including lower respiratory tract illness, gastroenteritis, and accidents are influenced by family stressors. The fact that a similar finding does not hold for asthma casts further doubt on the alleged psychosomatic basis of the condition.

Family social background and related factors were unrelated to risks of asthma in early childhood. This result is not entirely consistent with previous findings that New Zealand Polynesian children have a greater risk of asthma than white children.[30,31] The reasons for this difference are not clear, but it is possible that it arises from the age of the children being studied or from the fact that the majority of children nominally classified as Polynesian in this study had 25% or less Polynesian ancestry.[85]

Asthma afflicts a significant minority of the child population and its etiology is poorly understood. The search for social and familial correlates has led to a large and uneven research literature, suggesting the way in which various social and environmental factors may contribute to the development of asthma. This 6-year prospective study indicates that early childhood asthma appears to be inherited to some extent, its age of expression is related to the child's sex, and it has a complex interaction with other forms of allergic disease.[7] It is not related to infant feeding practices, smoking in the family, the presence of pets in the house, stress in the family, or the family's general social or economic situation. This is not to say that in individual cases these factors may not play a role in the development and onset of asthma, but rather that their role in contributing to the overall variations in the rate of the condition in the general child population (at least during early childhood) appears to be negligible. This would suggest that the etiologic basis of asthma is more likely to be found in studies of the genetic, physiologic, and immunologic basis of the condition rather than through an examination of the structure, practices, or dynamics of the family of the asthmatic child.

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ARE INTENSIVE CARE UNITS FUTILE?

[An] expert who worked for five years at a hospital in Cali, Colombia, told how the low-weight newborn mortality rate dropped greatly after an intensive care unit with all of the necessary equipment and trained personnel was opened at his hospital.

"But then we did a follow-up study to see what happened after the babies went home," he said "and we discovered that 75% of the infants were dead in six months from infections and malnutrition."

Submitted by Student

From Nelson H: Colombians 'pack' infants to mothers. *LA Times*, April 3, 1984.

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2024227820

Murray, A.B., Morrison, B.J. "The effect of cigarette smoke from the mother on bronchial responsiveness and severity of symptoms in children with asthma" J Allergy Clin Immunol 77(4): 575-581, 1986.

ABSTRACT. The effect of parental smoking was assessed in 94 consecutively observed children, aged 7 to 17 years, who had a history of asthmatic wheezing. The 24 children whose mothers smoked, when they were compared with children whose mothers did not smoke, had 47% more symptoms, a 13% lower mean FEV1 percent, a 23% lower mean FEF25-75%, and fourfold greater responsiveness to aerosolized histamine. A dose response was evident. There was a highly significant correlation between the results of the tests and the number of cigarettes the mother smoked while she was in the house. The differences between the children of smoking and nonsmoking mothers were greater in older than in younger subjects. The smoking habits of the father were not correlated with the severity of the child's asthma.

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The effect of cigarette smoke from the mother on bronchial responsiveness and severity of symptoms in children with asthma

Andrew B. Murray, M.B., F.R.C.P.(C), and Brenda J. Morrison, Ph.D.
Vancouver, British Columbia, Canada

The effect of parental smoking was assessed in 94 consecutively observed children, aged 7 to 17 years, who had a history of asthmatic wheezing. The 24 children whose mothers smoked, when they were compared with children whose mothers did not smoke, had 47% more symptoms, a 13% lower mean FEV_1 percent, a 23% lower mean $FEF_{25-75\%}$, and fourfold greater responsiveness to aerosolized histamine. A dose response was evident. There was a highly significant correlation between the results of the tests and the number of cigarettes the mother smoked while she was in the house. The differences betwen the children of smoking and nonsmoking mothers were greater in older than in younger subjects. The smoking habits of the father were not correlated with the severity of the child's asthma. (J ALLERGY CLIN IMMUNOL 77:575-81, 1986.)

Although cigarette smoke from parents is believed to increase wheezing among their children,[1] results from different surveys have been conflicting. In some studies parental smoking has no apparent effect[2,3]; in other studies greater frequency of wheezing is observed only if the mother smokes[4]; in yet other studies the prevalence of wheezing increases with the number of parents that smoke.[5] Similarly, spirometric values

Abbreviations used
$FEF_{25-75\%}$: Maximal midexpiratory flow rate between 25% and 75% of FVC
PC_{20}: Provocation concentration of histamine causing a 20% fall in FEV_1

From the Division of Allergy, Department of Pediatrics, and the Department of Health Care and Epidemiology, University of British Columbia, Vancouver, B.C., Canada.
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Reprint requests: Andrew B. Murray, M.B. B.C.'s Children's Hospital, 4480 Oak St., Vancouver, B.C., Canada V6H 3V4.

TABLE I. Comparability of groups

Features	Mother Nonsmoker	Mother Smoker	p Value (two-tailed)
	n = 70	n = 24	
Mean age (yr)	11.1	10.8	0.77
M:F ratio	21:14	19:5	0.15
Previous surgical operation*	27 (42%)	8 (38%)	0.94
More than three colds per year†	22 (49%)	9 (56%)	0.87
Gas stove in the kitchen‡	6 (12%)	2 (8%)	0.94
Dog or cat present	26 (49%)	11 (58%)	0.69
Any skin test positive	55 (79%)	21 (87%)	0.51
Mean diameter wheal to *D. farinae* (mm)	2.3 ± 0.4	1.6 ± 0.6	0.85

*Nine subjects were omitted from the analysis because of missing data.
†Thirty-three subjects were omitted from the analysis because of missing data.
‡Twenty subjects were omitted from the analysis because of missing data.

are variously reported as unaffected[2-6] or as slightly decreased, although significantly,[5, 7-9] when parents smoke.

These epidemiologic surveys have all been carried out on large representative groups of children. Because of this method of selection, those most likely to be affected by the smoke, the ones with asthma, were in the minority. In order to assess the effect of passive smoking on these more susceptible subjects, we examined a group of children who had a history of asthma or wheezing. Histamine bronchial challenge was performed in addition to spirometry because adults who themselves smoke may have increased bronchial responsiveness.[10, 11] Consequently, we suspected that children who are passive smokers might also have more irritable bronchi, resulting in an exacerbation of their wheezing.

METHODS

The study population consisted of 94 children, aged 7 to 17 years, who were referred consecutively to one of the authors for evaluation of suspected allergic disease and who had a history of wheezing or asthma. A trained interviewer asked the following standardized questions of the accompanying parents about the child's illness during the past 12 months: the frequency of wheezing, the frequency with which bronchodilator medications had been administered, whether or not corticosteroid tablets or corticosteroid aerosols had been used, and whether the child wheezed on exertion. Each feature in the history was assigned a range of scores; the scores for each individual were added to produce a summary rating called an asthma history score.[12] Children with no symptoms or medication for asthma during the previous year, for example, had a score of 0, and children with the most severe asthma had a summary score of 14 (Appendix). Inquiry was also made about other factors. The interviewer asked whether there was a gas cooking stove in the home, a device whose fumes might be irritating to the bronchi; whether there was a dog or a cat in the house, animals whose emanations might cause sensitization; whether the child had had a surgical operation, since the frequency of such a procedure might indicate the readiness with which the parents sought and followed medical advice; the number of colds in the past year, since respiratory infections themselves may precipitate and worsen asthmatic attacks; and, finally, the parents were asked how many cigarettes, cigars, and pipefuls of tobacco they smoked, both inside and outside the house. The child was asked privately whether or not he or she smoked.

Forced expiratory spirogram

Forced expiratory maneuvers were performed until there were three in which the FVC agreed within 5%. This was always achieved within five efforts. The tracing that had the greatest sum of FVC and FEV_1 was used for all measurements.[13] The FVC, FEV_1, and FEF_{25-75} were expressed as a percentage of predicted mean for age, sex, and height.[14]

The spirogram was recorded with a Pulmonor (Jones Medical Instrument Co., Oak Brook, Ill.) waterless spirometer that was calibrated weekly with a known volume of CO_2 discharged at a standard velocity from a calibrator instrument. The results of the tests were analyzed and printed by a Datamatic (Jones Medical Instrument Co.) computer that was connected to the spirometer.

Bronchial reactivity to histamine

Two days before the appointment, the parents were instructed to stop antihistamines and theophyllines and to administer no other bronchodilator medications for the 8 hours immediately before the visit, if it was possible. They were unable to stop medication in 23.1% subjects. A bronchial challenge test was not performed on these children nor on the children who reported a respiratory infection during the preceding 2 weeks, had an FEV_1 < 60% predicted or below 1L in volume, or were themselves smokers. The test was performed on the day on which they were first observed in all of the remaining 41 subjects.

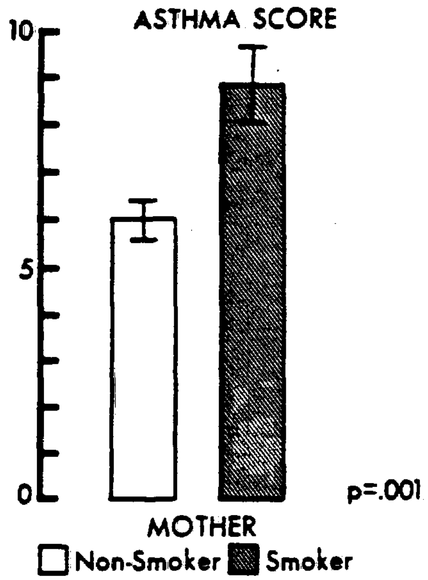

FIG. 1. The asthma history severity score, which ranges from a minimum of 0 to a maximum of 14, in two groups of children with a history of wheezing. The mothers of 69 were nonsmokers, and mothers of 23 were smokers. Means ± standard errors are presented.

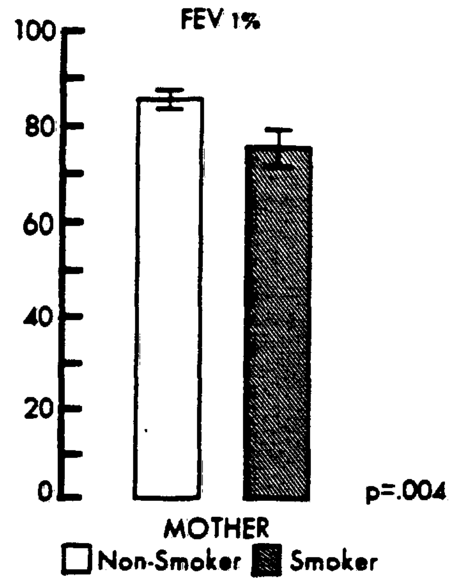

FIG. 2. The FEV_1 percent predicted in two groups of children with a history of wheezing. The mothers of 70 were nonsmokers, and mothers of 24 were smokers. Means ± standard errors are presented.

By use of a modification[12] of the method described by Cockcroft et al.,[13] each patient was administered doubling concentrations of histamine acid phosphate aerosol by mask, each inhalation session lasting for 2 minutes until PC_{20}. The strongest concentration administered was 8 mg/ml. Children whose FEV_1 did not decrease by 20% when this concentration was administered were deemed, for the purpose of calculating the mean PC_{20}, to respond to double that concentration, i.e., 16 mg/ml of histamine acid phosphate. There were two such subjects. The mothers were both nonsmokers.

Skin prick tests

By use of a standard method,[14] skin prick tests were performed on all subjects with negative and positive (histamine) control solutions, with 10% cigarette smoke (Bencard Division of Beecham Laboratories, U. K.), and with extracts of common inhalant and pollen allergens. The diameter of each resulting wheal was measured. If any wheal was 2 mm greater than that of the negative control solution, the test was regarded as positive and the patient as atopic. A 1% extract of *Dermatophagoides farinae* was included among those solutions tested, since the result would, if it were positive, be evidence not only of atopy but also of exposure to larger than usual numbers of house dust mites.[15]

The spirometric, bronchial challenge, and skin tests were performed by a technician who was unaware of the family's smoking habits.

Statistical method

Standard t tests were used to test differences between all quantitative variables except for those that were on a percentage scale, in which case a test of difference between normally distributed variates was applied. Pearson product-moment correlation coefficients were calculated as a measure of association.

RESULTS

The children were divided in the analysis into two groups on the basis of whether the mother did or did not smoke. These groups were comparable for age, gender, exposure to airborne irritants and allergens, percent that had had surgical operations, percent with frequent colds, proportion of subjects with atopy, and degree of sensitivity to house dust mites (Table I). The above mentioned variables were also comparable when the population was divided according to whether their fathers did or did not smoke.

Children of mothers who smoked had increased bronchial reactivity and worse asthma. Children whose mothers smoked had, on average, 47% more symptoms (Fig. 1), a 13% lower FEV_1 (Fig. 2), a 23% lower FEF_{25-75} (Fig. 3), and a fourfold greater responsiveness to aerosolized histamine (Fig. 4). All these differences between the two groups were highly significant (Table II). When the mean FVC percent

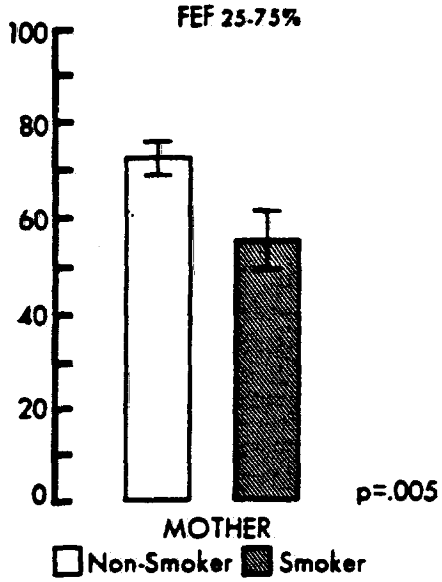

FIG. 3. The FEF_{25-75} percent predicted in two groups of children with a history of wheezing. The mothers of 70 were nonsmokers, and mothers of 24 were smokers. Means ± standard errors are presented.

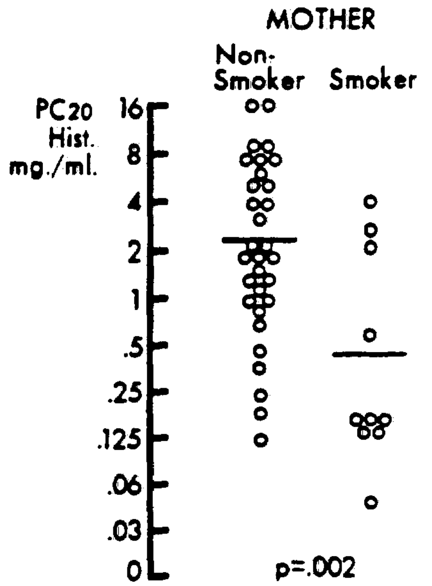

FIG. 4. The PC_{20} in two groups of children with a history of wheezing. The mothers of 32 were nonsmokers, and mothers of 10 were smokers.

predicted was examined, it was found not to be significantly different when the whole group of 94 subjects was considered. However, it was different in the subgroup of 41 subjects on whom the PC_{20} was performed, i.e., subjects whose values were not influenced by recent bronchodilator medications or by respiratory infections. In this subgroup the FVC was 85.2 ± 2.7% in children of mothers who smoked and 97.5 ± 18% in children of mothers who did not smoke ($p = 0.002$). We were therefore able to demonstrate a significant difference between the two groups in all tests of asthma severity that were applied.

A dose response to the mothers' cigarette smoke is also apparent both in the whole group of 94 and in the subgroup of 41 subjects. There was a significant correlation between the logarithm of the number of cigarettes the mother smoked while she was in the home and FVC, FEV_1, FEF_{25-75}, asthma history score and bronchial responsiveness to histamine (Table III). Not only was the correlation with bronchial responsiveness significant when all subjects with a baseline FEV_1 of 60% or more were included, but it remained significant ($p = 0.001$) when the analysis was restricted to subjects with a baseline FEV_1 of more than 70% predicted, the level usually accepted for histamine bronchial challenge testing.[13]

The effect of maternal cigarette smoke appears to be greater in older than in younger children, suggesting that not only the daily number of cigarettes but also the years of passive smoking increases the severity of its adverse effects. In children more than 11 years of age, there is, for example, a 19% difference in mean FEV_1 between the two groups, whereas in less than 11 years of age, the difference is only 9% (Table IV). Bronchial responsiveness in the older and younger subgroups could not be compared because it was assessed in only three of the older group whose mothers were smokers.

By contrast with the strong correlation between the mother's smoking habits and the severity of her child's asthma, there was no correlation between the number of cigarettes, cigars, or pipes of tobacco that the father smoked in the house and measures of lung function in the child (Table III); nor did the simple distinction of whether the father smoked or not smoked have any significant effect on any of the measurements (Table II). A partial explanation for the absence of effect may be the smaller number of cigarettes smoked at home by the father compared with the mother. Although the mean total of cigarettes that fathers smoked per day, 23, was slightly larger than that smoked by mothers, 18, the mean number that fathers smoked while they were in the house, eight, was significantly smaller than the number smoked in the house by mothers, 13.

Since there appeared to be no relationship between the smoking habits of the father and the severity of

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TABLE II. Difference in indicators of asthma severity between groups distinguished by smoking habits of the parents

	History score*	FEV_1 percent predicted	FEF_{25-75}	Geometric mean PC_{20}†	
Mother					
Nonsmoker (n = 70)	6.0 ± 0.4	85.5 ± 1.8	72.3 ± 2.8	2.2	n = 31
Smoker (n = 24)	8.8 ± 0.8	74.4 ± 3.7	55.6 ± 5.6	0.46	n = 10
P Value (two-tailed)	0.001	0.004	0.005	0.002	
Father					
Nonsmoker (n = 64)	6.9 ± 0.5	81.9 ± 2.1	67.0 ± 3.1	1.7	n = 26
Smoker (n = 28)	6.4 ± 0.6	84.4 ± 2.9	70.5 ± 4.9	1.2	n = 15
p Value (two-tailed)	0.5	0.5	0.5	0.4	
Parents					
Both nonsmokers (n = 51)	6.2 ± 0.5	84.7 ± 2.1	71.6 ± 3.2	3.1	n = 21
Either smokes (n = 43)	7.4 ± 0.6	80.3 ± 2.7	63.8 ± 4.3	0.8	n = 20
p Value (two-tailed)	0.11	0.2	0.15	0.001	

Means ± standard errors are presented.
*History score available for 92 children.
†PC_{20} measured on all 41 children who were eligible for the test. T tests were carried out on logarithm of the PC_{20} values.

TABLE III. Correlation (r) between indicators of asthma severity and the logarithm of the number of cigarettes smoked in the house by the parents and the probability (*p*) of r ≠ 0

	FVC (% Predicted)	FEV_1 (% Predicted)	FEF_{25-75} (% Predicted)	Log (PC_{20})	History score
Mother	r = 0.186	−0.300	−0.280	−0.482	0.224
	p = 0.039	0.002	0.004	0.001	0.018
Father	r = 0.036	0.028	0.001	0.075	0.084
	p = 0.367	0.395	0.495	0.319	0.218
Both parents	r = −0.081	−0.200	−0.227	−0.460	0.136
	p ± 0.228	0.031	0.017	0.001	0.107

the child's asthma, the influence of both parents smoking, considered together, was less than that of only the mothers smoking (Table II).

The prevalence of smoking among the children was low. Only two of them admitted to being smokers. The mother of the one smoked, and the mother of the other did not. The skin prick test to cigarette smoke was negative in all subjects.

DISCUSSION

We found, in a series of unselected consecutively referred children with wheezing, that asthma was more severe if the mother was a smoker. The decreases in spirometric values that we observed were larger than any previously reported. In these other studies, the decrease in mean values, although the decrease was significant in some children, did not exceed 5% in any of the children.[1] Vedal et al.,[8] for example, detected a 3% reduction in mean FEF_{25-75} in children whose mothers smoked. We found a 23% reduction.

[redacted] Previous studies have found a significant difference with some tests but not with other tests. It is likely that the greater differences, which we observed, result from studying a group of children who have asthma rather than children who are representative of the population at large. An additional new finding in our study was that the child's bronchial responsiveness increased if the mother was a smoker.

The evidence suggests that it is airborne cigarette smoke that causes the adverse effect. Not only is there a strong association between maternal smoking and severity of the child's asthma, but there is also evidence of a dose response. We found a significant correlation between all indicators of asthma severity and the logarithm of the number of cigarettes the mother smoked while she was in the home. There was also evidence that length of exposure had an effect. The

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TABLE IV. Differences in indicators of asthma severity between groups distinguished by age and by smoking habits of the mother

	History score*		FEV, % predicted		FEF$_{25-75}$ predicted		Geometric mean PC$_{20}$†	
	Age (>11 yr)	Age (<11 yr)	Age (>11 yr)	Age (<11 yr)	Age (>11 yr)	Age (<11 yr)	Age (>11 yr)	Age (<11 yr)
Mother Nonsmoker	6.6 ± 0.5	5.3 ± 0.6	84.5 ± 2.8	86.7 ± 2.2	73.6 ± 4.1	70.8 ± 3.7	2.3 n = 20	2.1 n = 11
Mother Smoker	10.1 ± 0.9	7.8 ± 1.2	68.7 ± 6.4	79.2 ± 4.0	52.0 ± 10.5	58.6 ± 5.6	0.4 n = 3	0.5 n = 7
p Value (two-tailed)	0.005	0.07	0.04	0.12	0.07	0.08	0.06	0.02

Forty-eight subjects were aged 11 years or older, and 46 were younger than 11 years. Means ± standard errors are presented.
*The history score was available for 92 children.
†The PC$_{20}$ was measured on 41 subjects.

older children, who had presumably been exposed to cigarette smoke for more years than the younger ones, were more severely affected. This finding is similar to that of Tager et al.[18] They reported that the normal rate of increase in FEV$_1$ during adolescent growth is slowed in children whose mothers smoked. Further evidence, that it is passively inhaled smoke that is responsible for the changes, is the effect observed when the mother stops smoking. Vedal et al.[8] report that children whose mothers are current smokers do but children whose mothers are exsmokers do not have significant differences in pulmonary function from those whose mothers are nonsmokers.

In contrast to the smoking habits of the mother, those of the father had no significant correlation with the severity of the child's asthma. These findings agree with those in more recently published large epidemiologic studies.[8,9] Several factors may account for this apparent paradox. One is our finding that the father, compared with the mother, smokes significantly fewer cigarettes when he is at home. Another is the possibility that the mother, more frequently than the father, is in the same room as the child when she smokes a cigarette. A third possibility is that the number of cigarettes smoked in the house are more accurately reported for the mother than for the father. The mother was usually the person who gave the information. Whatever the reason, the father's smoke did not appear to influence the child's asthma significantly. When we examined the effect of maternal and paternal smoking together, therefore, we found it to be less clear than when we examined the result of maternal smoking alone. This observation may explain the lack of effect of parental smoking on wheezing and spirometric values reported in some epidemiologic studies.[2,3,4]

It appears unlikely that greater exposure to respiratory infections or allergens was responsible for the increased severity of asthma in children whose mothers smoked. Comparable proportions in both groups had frequent colds, had a cat or a dog in the house, and had a positive skin test to an inhalant allergen. Furthermore, the skin prick test reaction to *D. farinae* was smaller, if anything, in the group whose mothers were smokers, and it did not appear that the mothers who were nonsmokers more readily sought medical advice for their children than did those who were smokers. The frequency of surgical operations was similar in the two groups; however, this possibility could not be excluded.

Why cigarette smoke should increase asthmatic symptoms is not known. One possibility is that bronchial epithelium is damaged, irritant receptors are stimulated, and bronchial responsiveness is increased.[19] Another possibility is that a specific allergen in tobacco leaf or smoke may be responsible. Lehrer et al.[20] explored this possibility but found no association between clinical symptoms from smoke and positive skin prick tests, precipitating antibodies, or specific IgE to tobacco smoke. Similarly, in our study, all skin prick tests to smoke were negative, but these findings do not exclude the possibility that the adverse effect of cigarette smoke is immunologically mediated. Two observations suggest that it may be. One is the presence of abnormally high IgE reported in adults who smoke[21] and in the children of smokers[22] and the other is an increased bronchial responsiveness, both in healthy adults who are smokers[10,11] and in our study population of children with asthma whose mothers were smokers. Increased responsiveness of the bronchi often results after the lung has been the site of an allergic reaction.[23] Burrows et al.[24] suggest ways, other than acting as a common inhalant allergen, in which tobacco smoke may elicit an allergic reaction in the lung.

Our findings indicate that maternal smoking aggra-

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vates asthma in children, the effect being clinically important as well as statistically significant. Paternal smoking was not related to the severity of the child's asthma, but a possible explanation for this is that most of the father's cigarettes are smoked when he is away from home. Physicians who observe children with asthma should ask the parents if they smoke. Parents that do smoke should be advised to stop smoking, at least when they are in their house.

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APPENDIX

History	Asthma history score*				
	0	1	2	3	4
Severity, parents assessment	None	Mild	Moderate	Severe	—
Days of wheeze	None	1 to 3	4 to 182	182 to 365	—
Days of medication	None	1 to 3	4 to 30	31 to 182	183 to 365
Corticosteroid medication	None	—	—	Yes	—
Wheeze on exertion	None	Yes	—	—	—

*Numerical score indicating severity assigned to each feature in the history.

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Anderson, H.R., Bland, J.M., Peckham, C.S. "Risk Factors for Asthma up to 16 Years of Age" Chest 91(6): 127S-130S, 1987.

SUMMARY: From a national cohort of 8,806 children examined at ages seven, 11 and 16 years (National Child Development Study), data on asthma or wheezing illness (AW) were analyzed to describe its natural history in childhood and its risk factors. Factors found to predict the subsequent onset of asthma included male sex of child, mother's age at the child's birth, pneumonia, whooping cough, tonsillectomy/adenoidectomy, allergic rhinitis, eczema and periodic abdominal pain/vomiting attacks. A wide range of perinatal factors, including feeding practices, and social and family factors were shown to have no effect on natural history.

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Risk Factors for Asthma up to 16 Years of Age*

Evidence from a National Cohort Study

H. R. Anderson, M.D.; J. M. Bland, Ph.D.; and C. S. Peckham, M.D.

From a national cohort of 8,806 children examined at ages seven, 11 and 16 years (National Child Development Study), data on asthma or wheezing illness (AW) were analyzed to describe its natural history in childhood and its risk factors. Factors found to predict the subsequent onset of asthma included male sex of child, mother's age at the child's birth, pneumonia, whooping cough, tonsillectomy/adenoidectomy, allergic rhinitis, eczema and periodic abdominal pain/vomiting attacks. A wide range of perinatal factors, including feeding practices, and social and family factors were shown to have no affect on natural history.

Much of the existing epidemiologic evidence about the etiology of asthma rests on prevalence and follow-up studies and there is a serious lack of population-based cohort data. The National Child Development Study (NCDS)[1] originated in the National Perinatal Study[2] and went on to become a multipurpose cohort study of child development including health. While it was not designed specifically to study the epidemiology of asthma, it is nevertheless possible to obtain valuable information relating to the natural history of asthma. This article describes some of the findings from our analysis of NCDS data which have implications for the etiology of asthma.

Materials and Methods

The NCDS followed-up at ages seven, 11 and 16 all children in England, Scotland and Wales born during one week of March, 1958. At each follow-up, information about current or past asthma or wheezing illness was obtained as part of a structured questionnaire on medical and other topics administered to parents by health visitors. The wording of the asthma questions varied at each interview but it was nevertheless possible to classify subjects at each interview into three categories: no asthma or wheezing, previous asthma or wheezing but not in the past 12 months, and current asthma or wheezing (symptoms reported in the past 12 months). Based on these three possibilities at each of three interviews, 27 mutually exclusive natural history categories can be created. Some of these contain small numbers or are of limited clinical or epidemiologic interest, and so for the purpose of the present analysis a collapsed classification of six natural history categories was used.

These natural history categories were analyzed in relation to medical and social data collected at each of the follow-up medical examinations and home interviews. Factors that have previously been reported to be associated with asthma or wheezing were selected together with those considered likely to influence the natural history of asthma.

The overall association between a variable and the natural history category was tested using the Chi-squared test or one-way analysis of variance as appropriate. Where there was a statistically significant overall association, the relative risks of each natural history category were calculated. The statistical significance of the relative risk was tested by calculating 95 percent confidence intervals.

*From the Department of Clinical Epidemiology and Social Medicine, St. George's Hospital Medical School, and the Department of Epidemiology, Institute of Child Health, London, England.
Reprint requests: Dr. Anderson, Clinical Epidemiology and Social Medicine, St. Georges Hospital Medical School, Cranmer Terrace, London SW 17 ORE, England

Table 1—*Lifetime Incidence of Asthma or Wheezing (n = 8,806)*

Age at interview (yrs)	Asthma or wheezing at any time in past (percent)	
	Cross-sectional	Cumulative*
7	18.3	18.3
11	12.1	21.9
16	11.6	24.7

*Using information from previous interviews

Table 2—*Prevalence of Asthma or Wheezing in 12 Months Preceding Interview (n = 8,806)*

Age at interview (yrs)	Asthma or Wheezing in past 12 months (percent)	
	Cross-sectional	Cumulative*
7	8.3	8.3
11	4.7	10.7
16	3.5	11.1

*Using information from previous interviews

Results

Data on asthma or wheezing were obtained at all three ages for 8,806 of the original NCDS cohort of over 15,000 children living in England, Scotland and Wales and available for follow-up at seven years.

The reported lifetime incidence of asthma or wheezing is shown in Table 1. Using data from all three interviews, a total of 24.7 percent of children had experienced asthma or wheeze by the age of 16 years. When questioned at age 16 years, however, the proportion reporting past asthma or wheeze was less than half this figure (11.6 percent). The prev-

Table 3—*Prognosis of Asthma or Wheezing if Current (past 12 months) at Age 7 (n = 731)*

Persistence of AW and age (yrs)	Percent of 7 year-olds who reported current AW
Current at 11	28.3
Current at 16	16.3
Current at 11 and 16	10.5
Current at 11 or 16	34.1
Not current at 11 or 16	65.9

Table 4—*Natural History Categories (n = 8,806)*

Category	Percent of sample
Never had asthma or wheezing	75.3
Onset before age 7 but not current at 7 or reported subsequently	8.6
Current at age 7 but not reported subsequently	5.5
Onset age 0 to 7 and also reported at 11 or 16	4.2
Onset age 8 to 11	3.6
Onset age 12 to 16	2.6

Table 5—*Factors Predicting the Onset of Asthma or Wheezing*

Predictive factors	Overall χ^2 P value	Relative risk of:	Natural history: By age 7 not after	At age 7 not after	Age 0-7 and after	Age 8-11 onset	Age 12-16 onset
Perinatal							
Sex of child	<0.001	Boy: girl	1.1	1.2	1.4*	1.3*	1.4*
Mother's age	<0.001	15-19: 20-29 yrs	1.4*	1.5*	1.1	1.9*	1.7*
		15-19: 30+ yrs	1.6*	1.3	1.3	1.9*	2.0*
		20-29: 30+ yrs	1.2	0.9	1.1	1.0	1.2
Smoking in pregnancy	<0.001	Smoker: Non-smoker	1.3*	1.2	0.8	1.0	1.0
Region of child's birth	<0.01	North: Centre	0.7*	0.9	0.9	0.7	1.0
		North: South	0.8*	0.9	1.0	0.9	1.0
		Centre: South	1.1	1.0	1.0	1.2	1.0
Assessed at 7							
History of pneumonia	<0.001	Yes: No	2.0*	2.0*	4.3*	1.5	1.8*
Tonsillectomy/ adenoidectomy	<0.001	Yes: No	1.3*	1.2	1.2	1.2	1.4*
Eczema in 1st year	<0.001	Yes: No	1.2	1.4	5.4*	1.7*	1.5
Eczema after 1st year	<0.001	Yes: No	1.1	1.3	4.7*	1.3	1.7*
Eczema on Dr. exam.	<0.001	Yes: No	0.8	1.1	4.9*	1.6	2.1*
Hayfever or sneezing ever	<0.001	Yes: No	1.3	2.0*	7.1*	1.5	1.7*
Periodic vomiting or bilious attacks ever	<0.001	Yes: No	1.2*	1.4*	1.8*	0.8	1.4*
Periodic abdominal pain ever	<0.001	Yes: No	1.4*	1.3*	1.5*	0.9	1.4*
Assessed at 11							
Whooping cough ever	<0.001	Yes: No	1.2*	1.3*	1.4*	1.4*	1.4*
Eczema in past year	<0.001	Yes: No	1.2	1.2	4.2*	1.9*	1.7*
Hayfever or allergic rhinitis in past year	<0.001	Yes: No	1.0	1.2	5.2	2.2*	1.9*

*$P<0.05$

alence of current asthma was highest at seven years (8.3 percent) but had fallen to 3.5 percent at 16 years (Table 2). At each interview, the lifetime and current rates for the present cohort (those with data available at all interviews) were similar to those among subjects interviewed only once or twice. Of those with current symptoms at seven, 28 percent reported current symptoms at 11 years, 16 percent at 16 years and 11 percent at both ages (Table 3).

For the purpose of analysis, the 27 patterns of questionnaire response were collapsed into the six categories described in Table 4.

From an etiologic standpoint two types of relationship could be discerned. In the first, a given factor was assessed prior to the onset of asthma or wheeze, and could therefore be considered predictive. In the other, the order of occurrence of the factor and the onset of asthma or wheezing could not, from the data available, be shown to be predictive because the assessment of both factors was concurrent. Most factors found to be predictive are shown in Table 5 together with their relative risks. Any concurrent associations for these variables are also shown. Of the perinatal factors the most prominent was sex of the child and the mother's age at birth of the child. Multifactorial analysis was done to explore whether social class or breast feeding might explain this latter relationship, but this was not the case.

Of the factors assessed at seven or 11 years, the main ones predicting subsequent onset of asthma or wheezing were atopic conditions—eczema or allergic rhinitis—and (at seven years only) periodic vomiting or abdominal pain. A history of pneumonia (at seven years) and whooping cough (at 11 years) were also predictive. Previous tonsillectomy or adenoidectomy reported at age seven years predicted onset in adolescence (though not when reported at 11 years).

Those factors which were concurrently associated with asthma or wheezing but not predictive are shown in Table 6. They mainly comprise upper and lower respiratory conditions but also include fits or convulsions in the first year (but not continuing into later life), enuresis, headaches and one adverse socioeconomic factor—sharing of one or more household facilities.

Those factors not associated with natural history are listed in Table 7. Notably, these included breast feeding, social class and a variety of indicators of socioeconomic circumstances and family stress.

Assessment of smoking in the household was inadequate, available only for the mother while she was pregnant and for both parents when the child was 16 years old. Smoking in pregnancy was associated only with an increased relative risk of asthma or wheezing during the early years of life and smoking by one or both parents reported when the child was 16 years was not related. At 16 years, the child's own smoking habit was unrelated to the presence of asthma or wheezing.

Discussion

The National Child Development Study was not designed to examine the etiology of asthma and there are a number of

Table 6—*Factors Concurrently Associated with Asthma or Wheezing but not Predictive*

Concurrent factors	Overall χ^2 P value	Relative risk of:	Natural history: By 7 not after	At 7 not after	0-7 and after	8-11 onset	12-16 onset
Assessed at 7 yrs.							
Household facilities	<0.008	Shared:not shared	1.1	1.5*	0.9	1.0	0.8
Whooping cough ever	<0.001	Yes: No	1.4*	1.2	1.4*	1.2	1.3
Throat/ear infections with fever, >3 in past yr	<0.001	Yes: No	1.2	1.6*	1.4*	0.7	1.0
Running ears ever	<0.03	Yes: No	1.3*	1.3	0.9	1.0	1.2
Fits or convulsions in 1st year	<0.001	Yes: No	1.2	1.8*	2.7*	1.0	0.6
Wet by day after 3 yrs	<0.004	Yes: No	1.2	1.7*	1.0	1.5	1.2
Wet by night after 5 yrs	<0.001	Yes: No	1.5*	1.2	1.0	1.2	1.1
Assessed at 11 yrs.							
Household facilities	<0.05	Shared:not shared	1.0	1.4*	1.1	0.8	1.1
Recurrent throat/ear infections in past yr treated by Dr	<0.001	Yes: No	1.1	1.0	1.5*	1.7*	1.1
Discharging ears in past year	<0.07	Yes: No	1.2	1.3	1.8*	1.6	0.7
Tonsils/adenoids removed	<0.001	Yes: No	1.2*	1.3*	1.2	1.2	1.0
Eczema on examination (Dr.)	<0.001	Yes: No	0.8	1.1	4.9*	1.6	2.1*
Recurrent headaches or migraine past year	<0.001	Yes: No	1.2	1.1	1.6*	1.2	1.1
Recurrent vomiting or bilious attacks in past year	<0.09	Yes: No	1.0	1.5*	1.3	1.5	1.0

*P<0.05

inadequacies in the nature and timing of both the assessment of asthma and wheezing and of etiologic factors. Against this is the advantage that these data relate to a national representative sample and contain a substantial number of subjects followed-up over a long time.

By including all children with reported asthma or wheezing, however mild, the present analysis may have missed associations that relate only to more severe asthma or wheezing, which is the main concern in medical practice. The data do, however, allow a simple grading of severity and this is being analyzed at present.

Considering the logistics of such a national cohort study, the response rate for information about asthma or wheezing on all three occasions of 59 percent of the original NCDS cohort could be judged as successful. Nevertheless, this raises the possibility of bias, which has been examined in detail.[2] It would appear that this is unlikely to have biased our results for relative risks or incidence and prevalence estimates. At any particular age, the prevalence rates among children for whom we had linked data were similar to the rates among those not seen on each occasion. The 12-month prevalence rates observed at age seven years were similar to those of other population surveys which have included all wheezing illnesses.[4-7]

As far as etiology is concerned, the most important findings in this study are those relating to factors which predicted or did not predict the later onset of asthma or wheezing. Among the perinatal factors, a new and possibly important finding was that the risk of all natural history categories apart from persistent asthma or wheezing (reported on all three occasions) was increased in children of mothers who were under 20 years of age at the birth of the child. This was independent of social class or breast feeding (which were

Table 7—*Factors Not Found to Be Predictive or Concurrently Associated with Asthma or Wheezing*

- Perinatal
  - Birthweight
  - Gestational age
  - Parity
  - Breast/bottle feeding
  - Birth order
  - Rank in family
  - Social class
- Assessed at 7
  - Crowding in household
  - Number of children in household
  - Tenure of accommodation
  - Social class
  - Separation from mother
  - In local authority care
  - Absence of one or more biological parents
  - Previous measles
- Assessed at 11
  - Previous measles
  - Social class
- Assessed at 16
  - Age at menarche
  - Pubic hair rating (boys)
  - Smoking of child
  - Smoking of parents

unassociated with natural history anyway). Further analysis found that the effect of maternal age existed within the 16 to 19-year-old age group as well. This finding needs to be confirmed by other studies and we can offer no plausible theory to explain it.

The increased risk of asthma or wheezing in boys agrees with other studies,[4] though our results differ from most in that the effect of male sex did not diminish as the age of onset of asthma increased.

The question of whether breast feeding protects against childhood asthma is of great importance since, if true, it would offer insights into etiology and a method of prevention. The evidence is patchy, but a prospective study by Blair[9] found that asthma was more likely to persist in those who were bottle fed. [redacted]

The association between natural history of asthma or wheezing and other atopic conditions confirms the abundant evidence from other prevalence and case-control studies. Additionally, however, we have demonstrated that periodic abdominal pain or vomiting attacks are also predictive and that headaches or migraine are an important concurrent association, though falling just short of significance as a predictive factor. Such associations have also been observed in a separate prevalence study[6] and can no longer be regarded as speculative. We feel that elucidation of the nature of these associations is an important research priority.

The last group of factors found to predict the onset of asthma or wheezing in adolescence were chest infections (pneumonia and whooping cough) and this finding has an important bearing on the question of whether and how early childhood chest troubles may predispose to chronic lung disease in later life as indicated in a previous prospective[10] and retrospective study.[11]

There are various explanations for the associations we have observed. The report of pneumonia or whooping cough may have been a mistaken diagnosis for what was in reality asthma. Chest infection may have led to the later onset of asthma by creating some predisposition which remained latent until adolescence. Both chest infections and asthma may have a common environmental cause or may be the result of a common predisposition via some kind of general "chesty" tendency. Perhaps the asthmatic tendency itself could predispose to chest infections and in some circumstances the chest infection might be expressed prior to the first attack of asthma.

Data about wheezing symptoms and chronic productive cough have been collected from this same cohort at the age of 23 years. Analysis of this additional information should provide further important evidence concerning the origins of both asthma and chronic bronchitis.

Conclusions

The National Child Development Study is an important source of nationally representative longitudinal data. While not specifically designed to study asthma, analysis of the data has elucidated a number of factors that predict the subsequent onset of asthma. These include male sex of the child, mother's age at child's birth, pneumonia, whooping cough, tonsillectomy/adenoidectomy, allergic rhinitis, eczema and periodic abdominal pain/vomiting attacks.

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Occupational Asthma

Moira Chan-Yeung, M.B., and Jean-Luc Malo, M.D.†*

This article reviews recent developments in the study of occupational asthma and implications for the overall understanding of asthma. Occupational asthma is a clinical syndrome caused by many different agents. Contribution of studies of experimental inhalation challenge using occupational agents to the knowledge of asthmatic reactions and their mechanisms is discussed. Investigations in the occupational environment into predisposing factors and persistence or recovery after exposure to an allergic agent or nonspecific irritant are reviewed. Approaches to diagnosing asthma in the occupational environment and to assessing functional impairment and disability are outlined. Directions for future research are identified.

Studies in occupational asthma have provided considerable insight into the various etiologic factors, possible pathogenetic mechanism and, to a certain extent, the clinical course of asthma. For the purpose of this presentation, occupational asthma will be defined as asthma caused by a

*From the Respiratory Division, Department of Medicine, Vancouver General Hospital, University of British Columbia, Vancouver.
†Department of Chest Medicine, Hôpital du Sacré-Coeur, Montreal, Quebec, Canada.

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Evans, D., Levison, M.J., Feldman, C.H., Clark, N.M., Wasilewski, Y., Levin, B., Mellins, R.B. "The Impact of Passive Smoking on Emergency Room Visits of Urban Children with Asthma" Am Rev Respir Dis 135: 567-572, 1987.

ABSTRACT. Baseline data obtained from a study of 276 children with asthma from 259 low income families were analyzed to test the hypothesis that passive smoking is associated with frequency of emergency room (ER) visits, hospitalizations, and impaired pulmonary function. The data were analyzed using multiple regression techniques. We controlled for other variables that might affect the frequency of ER visits, including smoking by the children themselves and the presence of other irritants or allergens in the child's home. Passive smoking was positively associated with ER visits ($p<0.01$), but not with hospitalizations or abnormalities in pulmonary function. The frequency of days with symptoms of asthma per month was also directly associated with ER visits ($p<0.02$). The estimated mean annual increase in ER visits attributable to the presence of one or more smokers in the household was 1.34 ± 0.50, an increase of 63% over nonsmoking households. The estimated annual health care cost for emergency care of children with asthma that can be attributed to passive smoking is 92 dollars (95% confidence interval from 24 to 160 dollars) for families with 1 or more smokers.

The Impact of Passive Smoking on Emergency Room Visits of Urban Children with Asthma[1-3]

DAVID EVANS, MOSHE J. LEVISON, CHARLES H. FELDMAN, NOREEN M. CLARK, YVONNE WASILEWSKI, BRUCE LEVIN, and ROBERT B. MELLINS

SUMMARY Baseline data obtained from a study of 276 children with asthma from 259 low income families were analyzed to test the hypothesis that passive smoking is associated with frequency of emergency room (ER) visits, hospitalizations, and impaired pulmonary function. The data were analyzed using multiple regression techniques. We controlled for other variables that might affect the frequency of ER visits, including smoking by the children themselves and the presence of other irritants or allergens in the child's home. Passive smoking was positively associated with ER visits (p [illegible]) but not with hospitalizations or abnormalities in pulmonary function. The frequency of days with symptoms of asthma per month was also directly associated with ER visits ($p < 0.02$). The estimated mean annual increase in ER visits attributable to the presence of one or more smokers in the household was 1.34 ± 0.80, an increase of 83% over nonsmoking households. The estimated annual health care cost for emergency care of children with asthma that can be attributed to passive smoking is 92 dollars (95% confidence interval from 24 to 186 dollars) for families with 1 or more smokers.

AM REV RESPIR DIS 1987; 135:567-572

Introduction

Passive smoking has been associated with a variety of harmful effects on children's lungs. These include increased occurrence of respiratory illness (1–6), impaired pulmonary function (7), and increased mortality (8). In addition, passive smoking has been associated with increases in visits to the physician (8), hospitalizations (8–10), and disability days (11).

On the basis of these studies, it is logical to expect that lungs hypersensitive to irritants may be even more vulnerable to the effects of passive smoking. Because asthma is a disease characterized by airways more reactive to irritants than normal, recent investigations have explored the impact of passive smoking on morbidity and pulmonary function in patients with asthma (12–18). Although the findings do not all demonstrate impaired health, there is evidence that passive smoking has harmful effects in children and adults with asthma, including increased incidence of asthma (12), exacerbation of symptoms (13), impairment of pulmonary function (16), and increased sensitivity to histamine (18). The effect of passive smoking on health care use by children with asthma, however, has not yet been studied.

We considered it important to examine this question because of the burden that frequent emergency room (ER) visits and hospitalizations for childhood asthma place on the family and the health care system (19, 20). Our study of the impact of health education on asthma management skills of the family and emergency health care use by children with asthma (21–23) provided an opportunity to study this question. We hypothesized that there would be a direct association between smoking by family members and the frequency of the child's ER visits and acute hospitalizations for asthma. In addition, we hypothesized that passive smoking would be associated with impaired pulmonary function.

Recognizing that factors other than passive smoking can also affect the frequency of health care use, we also explored the effect of 10 groups of variables that could influence this use (19–31). These factors, which are listed in *Appendix I*, were included in the data analysis to control for their effect on the relationship between passive smoking and health care use as well as to identify additional variables that might be influential.

Methods

Study Population

The study sample was composed of 276 children from 259 low income families who were receiving health care for asthma in outpatient clinics at 4 New York City hospitals. Children were enrolled in the study if they met all the following criteria: a diagnosis of asthma by a physician, at least 1 wheezing episode in the previous year, at least 1 clinic visit for asthma in the previous 12 months, and age between 4 and 17 yr. Informed, written consent was obtained from the child's parent. The study was approved by the institutional committee on human research. Fifty-five percent of the children were Hispanic, 38% were non-Hispanic blacks, and 7% were white, Asian, or native American. Sixty percent of the children were male, and the mean age was 9.9 ± 0.20 yr (unless otherwise indicated, the data are reported as the mean ± SEM). Ninety-three percent of the adult respondents to the enrollment interview were female and 67% of the households were headed by females. Sixty-three percent of the families received public assistance.

Because no community-wide survey was conducted, we do not know how well the study sample represents the general community population of low income children with asthma served by the 4 hospitals. Preliminary results from our own survey of families who had children with asthma attending public schools in the referral area of Babies Hospital (1 of the 4 hospitals in the original study), however, suggest that children in the clinic sample used the ER more frequently and were hospitalized more often than the children in the school sample. The clinic sample averaged 2.27 ± 0.21 ER visits per year, whereas the school sample averaged 0.86 ± 0.17 visits. This suggests that children in the current study may have more severe asthma and thus use

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[1] From the Department of Pediatrics, Columbia University College of Physicians and Surgeons, the Division of Biostatistics, Columbia University School of Public Health and Babies Hospital (Presbyterian Hospital), New York, New York, and the Department of Behavior and Health Education, University of Michigan School of Public Health, Ann Arbor, Michigan.

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[3] Requests for reprints should be addressed to Charles H. Feldman, M.D., Department of Pediatrics, Babies Hospital North, Room 107, College of Physicians and Surgeons, Columbia University, 630 West 168th St., New York, NY 10032.

emergency health care resources more frequently than the general community population of low income children with asthma.

There were 77 children (28%) in the study population who had missing data for 1 or more of the 3 variables in the final regression model; 8 additional children were eliminated from the analysis because they themselves were smokers. The results are reported for the remaining 191 children. We compared the children with missing data with those with complete data to explore the possibility of bias. The children with missing data made fewer ER visits (1.42 ± 0.30 versus 2.50 ± 0.24; $p < 0.01$), but did not differ from children with complete data with respect to passive smoking or frequency of symptom days. On sociodemographic indices, children with missing data were younger (6.6 ± 0.8 yr versus 9.9 ± 0.2 yr; $p < 0.01$), but did not differ from the others with respect to sex, ethnicity, or socioeconomic status. We have no evidence to suggest that the differences observed would create bias, i.e., a different relationship among the study variables in the 2 groups of children.

Variables

The data included in the analysis were drawn from several sources: separate baseline interviews with the child and with the child's parent or guardian, hospital records of emergency health care use in the year prior to the interview, and tests of pulmonary function. The ER visits and hospitalizations for asthma were counted by reviewing medical records of study children from the 4 participating hospitals. To examine the possibility that the study sample was making significant use of health services at hospitals not participating in the study, we reviewed Medicaid records of total health care use by the 88 families in the study who were receiving public assistance. Only 6 children (7%) made any ER visits and only 1 child (1%) was hospitalized in a nonparticipating hospital during the baseline year. We concluded that the hospital record review did not significantly underestimate ER use or hospitalizations for asthma.

Pulmonary function testing was conducted during a random clinic visit in the year after the baseline interview. A waterless wedge spirometer (Jones Medical Instrument Co.) was used to measure 3 factors: FEV_1, peak expiratory flow rate (PEFR), and mean forced expiratory flow during the middle half of the forced vital capacity (FEF_{25-75}). Each child repeated the measurement 3 times, and we used the highest values in the analyses. Data are reported both as raw scores and as a percentage of predicted normal values (32).

Passive smoking by the child was measured by asking the parent who was interviewed if he or she or anyone else in the house smoked. Passive smoking was given a score of zero if no one in the house smoked, and a score of 1 if the respondent or someone else in the house smoked. Data to measure the child's dose of passive smoking was not collected, nor was paternal or maternal smoking assessed. To control for active smoking we asked children, after guaranteeing confidentiality, if they ever smoked cigarettes, and the 8 children who said they did were removed from the analysis.

We did not obtain data on the presence or use of gas stoves. According to estimates by the public utility serving New York City, however, more than 99% of the families in our referral area use gas stoves. Therefore, it is unlikely that variations in nitrogen dioxide exposure because of the presence or use of gas stoves affected the frequency of ER visits.

Statistical Analysis

We used multiple regression techniques to test the hypothesis that passive smoking was associated with the frequency of ER visits and acute hospitalizations for asthma and with decreased levels of pulmonary function. A second goal of the statistical analysis was to discover whether any additional variables were significantly associated with health care use or with pulmonary function. A split sample procedure was used to evaluate the reliability of the ER visit model. The entire study population was randomly divided into 2 halves. Using the first half of the sample, we developed a regression model that fit the data best by minimizing the estimated standard deviation of regression. In addition to passive smoking, 34 other variables (see *Appendix 1*) were entered into the regression model using a backward elimination procedure. Because the number of variables was large in relation to the number of cases, the variables were entered sequentially in groups of 10 or less. The strongest predictors were retained and the weaker variables were eliminated until all the variables had been included in the regression and the best fitting model obtained.

The reliability of this model was evaluated by applying it to the data from the second half of the sample. We looked for consistency in the magnitude and direction of the regression coefficients across the 2 samples. The variables included in the final model had this consistency. Final values for the regression coefficients were obtained by applying the model to the full study sample. The association of specific variables with frequency of health care utilization was evaluated by the statistical significance of their regression coefficients in the final model using the full study sample. Statistical significance was defined as $p \leq 0.05$ using a two-tailed test.

There were 5 pairs of siblings among the 191 children who had complete data for the variables in the regression model; these siblings shared a common environment with respect to passive smoking and other variables. We assumed, however, that the emergency health care use and pulmonary function levels of siblings were statistically independent given the variables controlled in the model.

Because the distribution of ER visits was skewed toward the upper tail, we applied the square root transformation ($y = \sqrt{x}$) to approximately normalize the distribution. The regression analysis was conducted using the transformed scores. When final regression models using tranformed and untransforme ER visits were compared, there was no sig nificant difference in the coefficients of th predictor variables or in the distribution c the residuals, so for simplicity the finding are presented using untransformed scores

After the findings from the final regressio model were obtained, we examined the di tributions of the predictor variables and th residuals from the model. Observation of E visit frequency plotted against frequency c days with asthma symptoms per month ind cated that the relationship between these var ables was curvilinear. To adjust for this, w performed a logarithmic transformation c the symptom days score ($x' = \log [1 + x$ and found that the transformation improve the fit of the linear regression model to th data. We also tested for interaction betwee passive smoking and the frequency of sym tom days, but no interaction was found.

Upon examination of the residual scor (observed ER visits minus predicted ER visit from the normal regression model, we note that 9 cases (5%) were in a skewed upper ta of the distribution, more than 2 standard de ations above the mean. Because the norm regression model assumes normally distri uted errors, we explored other regressic models that allow skewed count data distr butions in order to assess the validity of th observed significance levels of the coefficier for passive smoking and days with asthn symptoms in the normal regression mod A geometric regression model was fitted the data by maximal likelihood estimatio and the results confirmed the significance the coefficients (33, 34).

We also conducted a path analysis (35, 3 to explore causal relationships among the va ables associated with ER visits. Path analy: is an interpretation of the relationships b tween the variables based on 2 assumptior (*1*) that a weak causal order among the va ables is known, and (*2*) that the relationshi among the variables are causally closed. weak causal order means that although X m or may not affect Y, Y cannot affect X. Cau closure means that X and Y are causally clos to systematic outside influence with respe to their covariation. The path coefficients a standardized regression coefficients obtain by regressing each variable in the model all the variables that are assumed to cau it. The logarithmic transformation of da with asthma symptoms was used in the pa analysis.

Results

Emergency Room Visits

Children in the study sample made a average of 2.50 ± 0.24 ER visits per ye The ER visits ranged from zero to 2 but 75% of the sample made 3 or le visits per year. The results of the regre sion analysis are presented in table Only 2 variables, passive smoking ar the frequency of days with asthma sym toms per month, were significantly

TABLE 1

REGRESSION COEFFICIENTS OF VARIABLES ASSOCIATED WITH ER VISITS*

Variable	b	SE	Beta	p Value
Passive smoking (x_1)	1.34 (b_1)	0.50	0.19	0.008
Days with asthma symptoms per month (x_2)	0.53 (b_2)	0.22	0.17	0.02
Constant	0.91 (a)	0.53		0.08

* n = 191; R^2 = 0.08; standard deviation of regression = 3.46; F = 8.11; df = 2,188; p = 0.003. The regression model is $y = a + b_1x_1 + b_2\log(1 + x_2)$, where y = number of ER visits; x_1 = passive smoking (1 if smokers present; 0 if smokers absent); b_1 = regression coefficient for x_1; x_2 = frequency of asthma symptom days per month; b_2 = regression coefficient for x_2; a = constant.

[redacted] Fifty-three percent of the adult respondents indicated that they or another household member smoked. [redacted] (table 1), [redacted]. The distribution of annual ER visits by children exposed to passive smoking is compared in figure 1 with the distribution of ER visits by children from households without smokers. The histogram shows the positive association between passive smoking and ER visits.

We explored the effect of recoding the smoking variable to reflect the presence of 2 or more smokers in the household. [redacted] The difference between these observed frequencies was not significant, and inclusion of this category of more intensive passive smoking exposure did not improve the fit of the regression model.

We were not able to assess directly the independent effects of mothers' and fathers' smoking behavior. Eighty-seven percent of the respondents, however, were either the child's mother or a female relative who had assumed the role of the child's principal caretaker. Because the father was often not present in the home, we reasoned that a comparison of smoking by the principal caretaker and by other people in the household would be an appropriate substitute for maternal and paternal smoking in this population. We eliminated the 24 cases in which the respondent was a male or was not the child's everyday caretaker, and compared the frequency of the child's ER visits in 3 groups: households in which the principal caretaker was the only smoker, households where only other people smoked, and households where both the caretaker and another person smoked. No sigificant difference was observed among the 3 categories of smoking exposure.

Children in the study sample had an average of 8.86 ± 0.76 days with asthma symptoms per month. The frequency of symptom days per month was also significantly associated with ER visits (table 1). This association was curvilinear: as symptom days increased, the corresponding increases in ER visits grew smaller. Children with low frequency (zero to 1 day) averaged 1.73 ± 0.33 visits; with moderate frequency (2 to 15 days), 2.65 ± 0.43 visits; with high frequency (16 to 31 days), 3.39 ± 0.60 visits. The distributions of annual ER visits by children with low, moderate, and high frequency of symptom days are shown in figure 2. The histogram shows the positive association between frequency of wheezing days and ER visits. [redacted] To evaluate these effects, we estimated a simple path model in which we assumed that passive smoking was an exogenous variable that had both a direct effect on ER visits and an indirect effect on ER visits through frequency of days with asthma symptoms. A path analysis of the effects of the variables in this model is presented in figure 3. [redacted] coefficient of 0.19. Passive smoking has

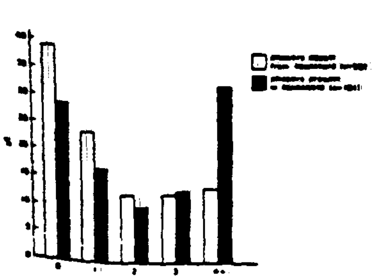

Fig. 1 Distribution of annual ER visits by presence or absence of smokers in the household. The 5 light bars sum to 100% of the children from nonsmoking households. The 5 black bars sum to 100% of the children from households with smokers. Note that 39% of the children with smokers absent made no ER visits compared with 29% of children with smokers present. In contrast, only 13% of children with smokers absent made 4+ ER visits compared with 32% of children with smokers present.

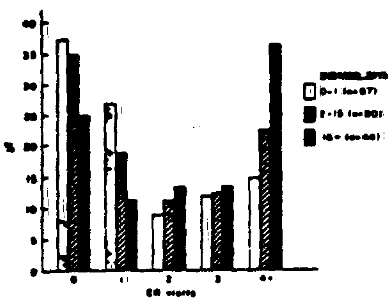

Fig. 2. Distribution of annual ER visits by frequency of asthma symptom days per month. Light bars sum to 100% of children with 0 to 1 symptom days, striped bars sum to 100% of children with 2 to 15 symptom days, and black bars sum to 100% with 16+ symptom days per month. Note that 37% of children with 0 to 1 symptom days made no ER visits compared with 25% of children with 16+ symptom days. In contrast, only 15% of children with 0 to 1 symptom days made 4+ ER visits compared with 38% of children with 16+ symptom days.

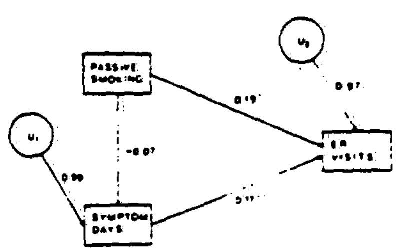

Fig. 3. A path model of the effects of passive smoking and frequency of asthma symptoms on ER visits. The path coefficients show the magnitude of the assumed causal effects indicated by the arrows. U_1 is the error term representing the unexplained variation in frequency of days with asthma symptoms; U_2 is the error term for ER visits; asterisk indicates p < 0.05.

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no significant effect on the frequency of days with asthma symptoms (−0.07) and no indirect effect through symptom days on ER visits (−0.07 × 0.17 = −0.01).

To rule out the possibility that the association of passive smoking with ER visits was due to some other variable, we conducted a regression analysis to identify any variables that might cause both increased smoking by family members and increased ER visits by the child with asthma. We found two—ethnicity and employment status—that had significant associations with smoking, but both variables had nonsignificant, inverse relationships with ER visits. Black families had more smokers than did Hispanic families, but made fewer ER visits. Families with 1 or more members employed full time had more smokers than did families without a wage earner, but also made fewer ER visits. Thus, neither variable had a significant effect on the relationship between passive smoking and ER visits.

To explore the possibility that nonsmoking parents were more health conscious and followed more careful preventive measures that resulted in fewer ER visits, we examined a subindex of preventive measures drawn from the index of family asthma self-management activities (23), but found no associations with passive smoking or with ER visits.

Hospitalizations

Seventeen percent of the children in the study sample had been hospitalized during the year prior to enrollment in the study; the mean number of hospitalizations was 0.20 ± 0.04. Passive smoking was not significantly associated with annual frequency of hospitalization. Only 2 variables, the number of the child's siblings with asthma (regression coefficient, 0.16; $p < 0.05$) and the frequency of missed outpatient clinic appointments (regression coefficient, −0.21; $p < 0.01$), were significantly associated with hospitalizations.

Pulmonary Function

The mean value for %FEV_1 in the study sample was 72 ± 2%. The mean pulmonary function scores presented in table 2 indicate that passive smoking did not have a significant effect on any of the 3 indicators of pulmonary function studied. A regression of %FEV_1 on the variables measuring sociodemographic status, disease characteristics, allergens and irritants in the home, and familial history of asthma indicated that none of these factors was significantly associated with %FEV_1.

TABLE 2

MEAN PULMONARY FUNCTION SCORES BY PRESENCE OR ABSENCE OF SMOKERS

	Smokers in Household		
Test*	Absent (n = 59)	Present (n = 89)	p Value†
FEV_1, L	1.49 ± 0.09	1.80 ± 0.08	NS
%FEV_1	72.06 ± 2.38	71.71 ± 1.82	NS
PEFR, L/s	2.74 ± 0.19	3.19 ± 0.18	NS
%PEFR	74.03 ± 3.54	78.87 ± 2.96	NS
FEF_{25-75}, L/s	1.42 ± 0.10	1.80 ± 0.10	NS
%FEF_{25-75}	58.87 ± 3.88	61.22 ± 3.59	NS

* For each test the first line reports the mean ± SEM of the raw scores and the second line reports the raw scores as a percentage of predicted normal values (32).

† One-way analysis of variance.

Health Care Costs

To assess the impact of passive smoking on health care costs for children with asthma, we estimated the cost of an ER visit to the participating hospitals during the study period. The average cost of an ER visit, including medications, was 69 dollars. Multiplying this cost by the number of additional ER visits attributable to smoking (1.34 ± 0.50, with 95% confidence interval from 0.36 to 2.32), the estimated additional health care cost for emergency care for asthma was 92 ± 68 dollars per year (95% confidence interval from 24 to 160 dollars) for families with 1 or more smokers in this low income, urban, minority population.

Discussion

The association between smoking in the child's home and the frequency of ER visits is based on parents' reports of smoking behavior and should be interpreted with some caution. No objective evidence of smoking behavior by household members was collected, nor was any attempt made to demonstrate that children had significant levels of exposure to tobacco smoke. The proportion of respondents in the study sample who said they smoked (34%) is identical to the proportion of smokers among females between 21 and 44 yr of age reported in a recent nationwide survey (37). If, in fact, some respondents who did smoke concealed this information, the effect would be to diminish the observed association between smoking and ER visits.

The association between passive smoking and ER visits is a strong one. The presence of even 1 smoker in the household increased the annual frequency of the child's ER visits by 63%. The fr quency of days with asthma symptor per month was also significantly a sociated with ER visits. There was, hov ever, no relationship between passi smoking and the frequency of days wi asthma symptoms. This finding is pu zling because one mechanism by whic passive smoking can increase ER visi is by increasing the frequency of symp toms, and it raises the question o how passive smoking affects ER vis frequency.

One possibility is that there are meas urement errors in parents' perception o the child's symptoms. Low level asthm symptoms may be difficult to notice, o like other common symptoms, may sim ply be taken for granted and thus under reported. An alternative possibility is sug gested by the well-established finding tha people with asthma can have air-flow obstruction without experiencing symptoms of breathlessness, and that at any given level of obstruction, reports of breathlessness vary considerably (38–40). Children themselves may not notice or report symptoms to their parents, thus obscuring the association between passive smoking and chronic symptom frequency. Furthermore, in a study of adults with asthma, Burdon and coworkers (40) found that patients with increases in baseline air-flow obstruction—a characteristic of our sample with mean %FEV_1 equal to 72%—were less able than patients with normal baseline air flow to detect breathlessness in response to a histamine challenge.

Recent findings that link passive smoking, histamine reactivity, and reduced perception of breathlessness, however, suggest a more complete explanation for the association of passive smoking with ER visits without a corresponding increase in chronic symptoms. First, Knight

and Breslin (18) found that experimentally controlled passive smoking increased sensitivity to histamine challenge in patients with asthma after a 4-h period, well after pulmonary function returned to normal. They suggest that passive smoking sensitizes the airways to react more strongly to other sources of irritation and thus potentiates acute episodes that would not otherwise have occurred. [redacted] Thus, in the absence of other asthma triggers that start an acute episode, the frequency of reported symptoms may decrease among children chronically exposed to tobacco smoke. We speculate that if another trigger does provoke an acute episode, the reduction in ability to recognize breathlessness is likely to result in delayed treatment, thus adding to the severity of the episode and the likelihood of eventually requiring emergency medical treatment. [redacted] This finding is not inconsistent with the mechanism proposed above because increased reactivity to histamine challenge is often present in patients with normal baseline pulmonary function (41). The lack of association between passive smoking and hospitalizations, however, does raise questions about the proposed histamine reactivity mechanism because heightened airway reactivity and reduced awareness of breathlessness would result in more severe episodes that receive delayed treatment; this in turn would be expected to result in increased hospitalizations.

[redacted] Health care providers can help prevent ER visits among children with asthma, and thus reduce health care costs, by explaining the association between smoking and ER visits to family members, encouraging them not to smoke, and referring them to smoking cessation programs. Although we have no direct evidence that passive smoking heightened airway reactivity or reduced recognition of breathlessness in our study sample, such changes, if present, would provide a plausible explanation for our findings. We think that research to explore these possibilities is worthwhile.

Appendix 1

Additional variables included in the analysis:

I. An index of allergens and irritants in the home.

II. Parents' report of the child's average monthly frequency of days with symptoms of asthma.

III. Family management practices.
- Frequency of problems adhering to medication schedule.
- Frequency of missed clinic appointments.
- An index of self-management activities used to control asthma.
- An index of criteria for deciding if medical help is needed to manage asthma symptoms.
- Parents' level of confidence in ability to manage asthma.

IV. Coverage of child by Medicaid.

V. Nonemergency care.
- Parents' rating of acceptability of outpatient clinic waiting time.
- Parents' satisfaction with amount of information about asthma provided by outpatient clinic physician.
- Continuity of care in clinic.
- Frequency of parents' questions to physician.

VI. Sociodemographic variables.
- Sex of child.
- Age of child.
- Age of parent/guardian.
- Ethnicity/race.
- Employed person in household.
- Mother's employment status.
- Mother's years of education.
- Mother's marital status.
- Number of people in household.
- Number of people per room.
- Telephone in household.
- Change of residence in last five years.

VII. Health beliefs.
- Health locus of control scale.
- Effectiveness of medicine in preventing attacks.
- Seriousness of child's asthma.
- Belief that mild attacks require hospital or clinic visit.
- Belief that asthma is more frightening than other diseases.
- Belief that asthma can lead to other health problems.

VIII. Social support.
- Number of adults in household who help care for child's asthma.

IX. Stress during asthma attacks.
- Parental fear child might die during most recent attack.

X. Family history of asthma.
- Parental history of asthma.
- Siblings with asthma currently.

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Toyoshima, K., Hayashida, M., Yasunami, J., Takamatsu, I, Niwa, H., Muraoka, T. "Factors influencing the prognosis of wheezy infants" J Asthma 24(5): 267-270, 1987.

ABSTRACT. Forty-eight wheezy infants were followed up for 25 to 44 months. These infants were classified into three groups: those with asthma (developed asthma later), the wheezy group (had successive wheezing episodes), and the non-wheezy group (grew out of the wheezy episodes).

Serum IgE levels at the first visit were not significantly different in the three groups, but the frequency of exposure to cigarette smoke was higher in the asthma and wheezy groups than in the nonwheezy group.

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Factors Influencing the Prognosis of Wheezy Infants

Kyoichiro Toyoshima, M.D.,* Michiaki Hayashida, M.D.,* Jun Yasunami, M.D.,* Isamu Takamatsu, M.D.,* Hisao Niwa, M.D.,* and Tetsuji Muraoka, M.D.†

*Department of Pediatric Allergy
Osaka Prefectural Habikino Hospital
3-7-1, Habikino
Habikino City
Osaka 583, Japan
†Muraoka Pediatric Clinics
Fujiidera, Osaka, Japan

ABSTRACT

Forty-eight wheezy infants were followed up for 25 to 44 months. These infants were classified into three groups: those with asthma (developed asthma later), the wheezy group (had successive wheezing episodes), and the non-wheezy group (grew out of the wheezy episodes).

Serum IgE levels at the first visit were not significantly different in the three groups, but the frequency of exposure to cigarette smoke was higher in the asthma and wheezy groups than in the nonwheezy group.

INTRODUCTION

Most wheezy infants grow out of wheezing episodes in childhood. But some wheezy infants will have recurrent wheezing attacks in childhood or become asthmatics.

It is important for clinicians to anticipate the prognosis of the wheezy infants, if possible. We followed up the wheezy infants for a couple of years, and we were aware of the fact that passive smoking worsens the prognosis of wheezy infants.

MATERIALS AND METHODS

We selected 65 nonfebrile wheezy infants less than 3 years old who had no dyspnea

typical of asthma. The questionnaire (Figure 1) was filled out by the doctors during the interview with the mothers. At the first visit, venous blood was drawn for hematology and determination of serum IgE. The state of wheezing was reevaluated 25 to 44 months later by examining the medical chart or by telephoning the mothers. Reliable information was obtained in 48 cases (33 boys, 15 girls).

Serum IgE levels were assayed by the ELISA method with the Phadezyme Kit (Pharmacia). Serum IgE levels were compared with the old matched mean value for healthy infants by Furukawa et al. (1), and the level was judged as high when the level was a standard deviation higher than the mean value, and extremely high when the level was two standard deviations higher than the mean value.

The infants who had more than 5% peripheral blood eosinophils were diagnosed as eosinophilic.

Comparability of the groups was evaluated by the chi square test, Fischer's exact test, or Student's t test.

RESULTS

The mean age at the first visit was 14.9 ± 8.6 months (mean ± SD). The infants were

Name Sex M. F. Birthday__________
Date Age
IgE (ELISA): IU/ml
Hematology WBC: Eo: %

1. Major allergy in relatives: + − (Atopic dermatitis / Asthma, rhinitis / Recurrent urticaria)
2. Minor allergy in relatives: + − (Urticaria / Adverse drug reaction)
3. Past history of wheezing: + − Initial age: Season:
4. Allergic past history
   Eczema: + −, Allergic rhinitis: + −, Recurrent urticaria: + −
5. Past history of food allergy: + −
6. Fever with wheezing: + −
7. Birth weight: g
8. Disturbances at birth: + − ( )
9. Start of formula milk: month(s)
10. Start of fruit juice: months
11. Feeding method: breast formula
12. Vaccination history:
13. Symptoms at first visit: Wheezing (+ −), Fever (+ −)
14. Smoking habits in family: Father (++ + −), Mother (++ + −), Others (++ + −)

Figure 1. Questionnaire completed in interviews with the mothers of the wheezy infants.

classified into three groups: The first (the asthma group) included 12 wheezy infants who were diagnosed later as asthmatic. The second group (wheezy) comprised nine wheezy infants who still had wheezing episodes in the last year of the observation period. The third group (nonwheezy) included 27 infants who had no wheezing episodes in the last year of the observation period. The infants' mean age did not differ significantly between the groups (Table 1).

The findings in each group are summarized in Table 2. The statistical differences between the groups were calculated. Hyperglobulinemia E levels, family history of allergy, history of wheezing and of allergic diseases, disturbances at birth, breast feeding, and fever episodes with wheezing were not different statistically between the groups. Eosinophilia was more frequent in the asthma group than in the other groups. Infants in the asthma and wheezy groups lived with family members who smoked heavily. The mean age when the initial wheezing episode occurred was greater in the asthma group than in the other groups.

Table 1. Mean Age of Each Group

GROUP	INFANTS	MEAN AGE (mo)
Asthma	12	18.3 ± 9.4
Wheezy	9	14.0 ± 7.1
Nonwheezy	27	13.7 ± 8.5

DISCUSSION

Some investigators have reported that IgE levels in cord blood or in infants predict the development of atopic diseases in later life (2–4). Our findings show that IgE levels in wheezy infants do not predict the development of asthma or continuation of wheezing episodes. On the other hand, eosinophilia was more frequent in the asthma group than in the other groups. Considering these two findings, asthma may develop through a non-IgE-mediated allergic process. But this cannot be concluded only by our findings.

Table 2. Clinical Features of Each Group

	HIGH IgE	EXTREMELY HIGH IgE	EOSINOPHILIA	FAMILY HISTORY	HISTORY OF WHEEZING	HISTORY OF ALLERGIC DISEASES
1. Asthma group	5/11	1/11	6/11	8/12	9/12	7/12
2. Wheezy group	4/8	2/8	0/7	6/9	8/9	4/9
3. Nonwheezy group	6/26	4/26	2/24	12/27	20/27	10/27
Differences						
(1 + 2)/3	NS	NS	$p = 0.05$	NS	NS	NS
1/2			$p = 0.025$			
1/3			$p = 0.006$			

	DISTURBANCE AT BIRTH	FORMULA MILK < 1 mo OLD	SMOKING IN FAMILY	FEVER WITH WHEEZING	AGE OF INITIAL WHEEZING (mo)
1. Asthma group	1/12	6/11	9/10	2/11	14.5 ± 8.7
2. Wheezy group	2/9	3/9	8/8	1/9	9.0 ± 6.0
3. Nonwheezy group	3/27	13/26	13/22	5/26	8.1 ± 8.1
Differences					
(1 + 2)/3	NS	NS	$p = 0.01$	NS	
1/2					$p < 0.1$
1/3					$p < 0.05$

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The fact that parental smoking affects childhood airway diseases has been reported by others (5,6). But it is not clear whether parental smoking increases the morbidity of infantile asthma. Our findings showed that the infants in smokers' families had successive wheezing episodes or developed asthma more frequently. Accordingly, we can conclude that passive smoking inhibits the outgrowing of wheezing in infants. We could not identify the mechanism by which passive smoking affected the infantile airways, but we should advise the families whose infants have wheezing episodes to stop smoking.

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Kershaw, C.R. "Passive smoking, potential atopy and asthma in the first five years" Journal of the Royal Society of Medicine 80: 683-688, 1987.

SUMMARY: Evidence of prolonged exposure to cigarette smoke was sought in a group of 86 children aged five years and under with moderately severe asthma, and in 1199 infants from a mixed background population of Armed Service and civilian families. Asthmatics with a normal serum IgE (less than + 1s.d. for age) made up almost half of the cases, and, compared with those with an elevated serum IgE (+ 1s.d. for age or more), a greater proportion were male, had experienced prolonged exposure to cigarette smoke, were from Service families and already had fixed chest deformity. It is suggested that, in addition to facilitating the expression of asthma in young potential atopics, passive smoking may be an important contributory cause of the more severe disease reported in the so-called 'intrinsic' group. Perhaps the burden of illness and the extent of exposure noted in this survey will prompt renewed efforts to be made to discourage smoking in families, particularly two years before and for at least five years after the birth of a child.

Passive smoking, potential atopy and asthma in the first five years

C R Kershaw MRCP DCH Royal Naval Hospital, Haslar, Gosport, Hampshire

Keywords: asthma, passive smoking, armed services, atopy, chest deformity

Paper read to Section of Paediatrics, 16 April 1985

Summary

Evidence of prolonged exposure to cigarette smoke was sought in a group of 86 children aged five years and under with moderately severe asthma, and in 1199 infants from a mixed background population of Armed Service and civilian families. Asthmatics with a normal serum IgE (less than +1 s.d. for age) made up almost half of the cases and, compared with those with an elevated serum IgE (+1 s.d. for age or more), a greater proportion were male, had experienced prolonged exposure to cigarette smoke, were from Service families and already had fixed chest deformity. It is suggested that, in addition to facilitating the expression of asthma in young potential atopics, passive smoking may be an important contributory cause of the more severe disease reported in the so-called 'intrinsic' group. Perhaps the burden of illness and the extent of exposure noted in this survey will prompt renewed efforts to be made to discourage smoking in families, particularly two years before and for at least five years after the birth of a child.

Introduction

Passive parental smoking has been shown to be linked to respiratory infections, impaired lung development and bronchial lability during vulnerable periods in a child's growth and acquisition of immunity[1-4]. Despite the fact that passive smoking could well be the most important 'non-communicable' environmental factor involved in the aetiology of early asthma, only recently does it appear that a detailed account of this aspect of the child's early environment has been considered in prospective surveys of asthma following lower respiratory tract infections[5,6]. Even now, the extent to which passive smoking affects the severity and natural history of either atopic or non-atopic (perennial or 'intrinsic') asthma in small children is unclear.

Although the prevalence of parental smoking has shown a gradual decline in the past decade, the rate of fall is sex and social class related and there is evidence that the overall percentage of smokers and of smoking parents in South East Hampshire has generally been higher than in England and Wales as a whole[7]. There is also some evidence that parents of asthmatic children at age 15 years smoke less than the general population[8]. However, both at the Royal Naval Hospital, Haslar, and in the local community, the opposite was observed, i.e. the parents of very young children with a variety of obstructive airways diseases were often active smokers.

The aim of the present survey was therefore to define a population of young, more severe asthmatics and compare smoking behaviour in their parents with that of the general background population of parents locally in the Portsmouth area. At the same time, a more detailed assessment of atopic potential, immunization status, and chest deformity was undertaken in the asthmatic children.

Methods

Data on the background population were obtained by Gosport health visitors who enquired about regular smoking in both parents and other resident members of the household at the four-week examination for all children born in Gosport from April 1983 to March 1984 inclusive. This information was routinely collected as part of a multi-centre risk-related sudden infant death syndrome intervention study. An active smoker was defined as one who regularly smoked more than 5 cigarettes a day. A similar format of enquiry was used to ascertain those who had been resident in the household of asthmatic children and who had been active smokers for more than 50% of the child's first three years of life. An asthmatic was defined as any child under the age of six who had had three or more bouts of bronchitis or bronchiolitis (persisting cough and/or wheeze with illness lasting for 48 hours or more) in any six-month period and who in addition had had either definite intermittent wheeze or chronic night cough. This definition was used prospectively to screen all children referred to hospital with respiratory illness between April 1983 and January 1985, and the group thus comprised a consecutive series of young children with moderately severe asthma.

At the time of enrolment a careful enquiry was made by the author of family history of atopic symptoms in first-degree relatives, the number of previous admissions to hospital for chest problems and pertussis immunization status. An assessment was made of any chest deformity. Unless there was already clear and reproducible evidence of associated allergic eczema or urticaria, blood was taken for estimation of serum IgE and IgE antibodies to house-dust mite, grass, tree and weed pollens, and cat and dog (epithelium). Convalescent venous samples were taken when no oral steroid medication had recently been prescribed.

Atopic potential was thus assessed in three separate ways: in terms of the presence or absence of (1) a personal history of allergic eczema or urticaria; (2) a first-degree family history of atopic conditions; and according to (3) the level of a single convalescent estimation of serum IgE. Children regarded as having potentially non-atopic or 'intrinsic' asthma tended to show negative family histories, but, in particular, their serum IgE was less than 1 s.d. above the mean for age.

Results

In the 22-month period, 91 consecutively referred children aged under six years met the criteria for definition of asthma used for this survey. Comparison

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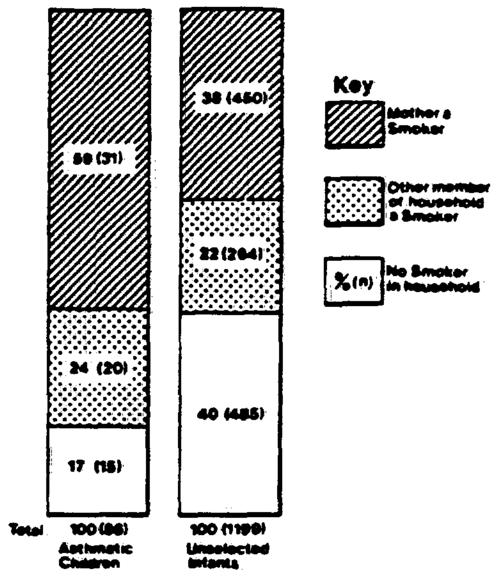

Figure 1. Prevalence of smoking in households of asthmatic children

with Ward diagnostic index and hospital statistics suggests that this group represented approximately one-quarter of all children seen with lower respiratory tract symptoms over the period and contained the majority of those with perennial and more severe illness. Five had persisting symptoms and signs and further investigations revealed specific diagnoses, namely: cystic fibrosis (1M, 1F), tracheo-oesophageal fistula (1M), congenital collapsing left main bronchus with hypoplastic left lung (1M), immotile cilia syndrome (1M). The remaining 86 (57M, 29F) had asthma with a mean age at ascertainment of two years and seven months, by which time they had already had a mean of 2.15 admissions per child. In 9 of these children the presence of atopic eczema, a positive family history of atopy in first-degree relatives, and reproducible allergic reactions or positive skin tests in the child strongly suggested atopy, and serum IgE measurement was not undertaken. This group was, however, included in the comparison of the prevalence of smoking in members of the household with that in the background population.

Prolonged exposure to cigarette smoke

The results of the comparison of prevalence of smoking in the household are shown in Figure 1. The prevalence of smoking was clearly higher in the households of asthmatic children than in the background population. When the differences in prevalence of smoking are broken down according to the father's occupation, as in Table 1, it is evident that the major difference between the Service and civilian populations lies in the greater proportion of members of households smoking in the Service asthmatics families (87% cf. 79%). Significance ($\chi^2_{(1)}=11.0$, $P<0.01$) for this group was the highest of the four sub-groups, all of which showed increased prevalence of smoking in the households of asthmatic children, compared to the background population.

Table 1. Prevalence of smoking in relation to father's occupation

	Armed Service		*Civilian*	
Mother a smoker:				
Asthma	23 (59%)	$\chi^2_{(1)}=6.4$; $P<0.05$	28 (60%)	$\chi^2_{(1)}=7.8$; $P<0.01$
Unselected	221 (37%)		229 (38%)	
Member of household a smoker:				
Asthma	34 (87%)	$\chi^2_{(1)}=11.0$; $P<0.01$	37 (79%)	$\chi^2_{(1)}=5.6$; $P<0.05$
Unselected	350 (59%)		364 (60%)	

Percentages refer to proportion of all service or all civilian

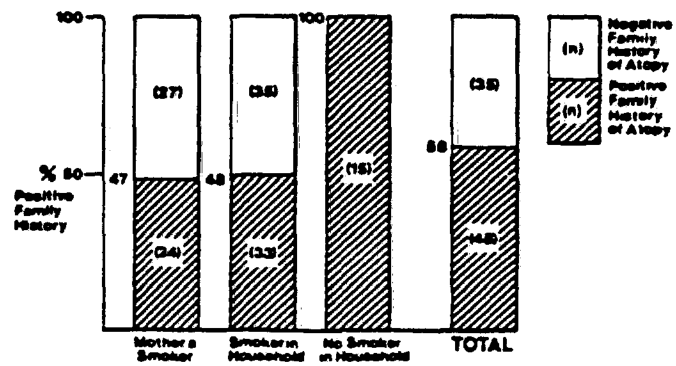

Figure 2. Smoking in households of asthmatic children in relation to family history of atopy

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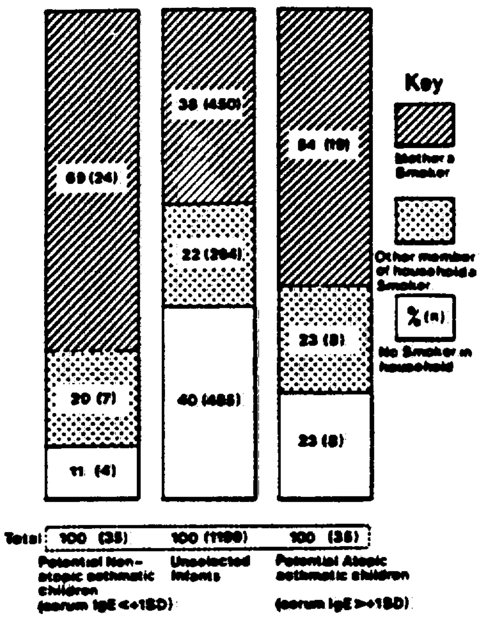

Figure 3. Prevalence of smoking in relation to atopic potential

Table 2. Pertussis immunization uptake for asthmatic children

	%	(n)
Potential non-atopic (serum IgE < + 1 s.d.)	52	(27)
No smoker in family	50	(14)
Civilian family	46	(39)
Asthmatic children (all)	42	(69)
Member of household a smoker	39	(54)
Service family	37	(30)
Potential atopic (serum IgE > + 1 s.d.)	35	(31)

Atopic potential

Family history: Information on family history of atopy in first-degree relatives was available in 83 of the 86 cases. From the data in Figure 2 it can be seen that in the absence of a positive family history, all the asthmatic children's households contained at least one member who was a regular smoker. All the non-smokers occurred in association with a positive family history of atopy, but even a personal or close family history of asthma did not appear to have discouraged smoking in the parents of many of these young asthmatic children.

Serum IgE: A single level of serum IgE was available for 70 of the 77 asthmatic children in whom atopic status was uncertain, but was unavailable in 7 either because they had moved from the area or defaulted the clinic.

The mean age of measurement of serum IgE in this survey was 2 years 11 months. On the basis of the single serum IgE measurement, 35 (50%) of the children tested were regarded as potentially atopic and an equal number potentially non-atopic. It can be seen from Figure 3 that a similar trend emerges, with the higher prevalence of active smoking occurring consistently in the households where the asthmatic child was potentially non-atopic. Differences between the potentially atopic and non-atopic households did not reach significance, but both of the groups with measured serum IgE showed significant differences when compared to the background population.

Pertussis immunization

For 69 of the 86 cases there was good recall of data on pertussis immunization status. The British Paediatric Association Immunization Committee's figures for pertussis vaccine uptake in the first three years of life (for 1982) are 53% for England and 59% for Wessex Region. Table 2 shows the comparison between the different sub-groups, with only 42% overall achieving positive status, i.e. in date with all scheduled immunizations. Thirty-three of this group of asthmatics (48%) had the double disadvantage of living in a household where there was an active smoker and being inadequately protected against pertussis.

Chest deformity

Seventy-one children were carefully examined by the author for evidence of fixed chest deformity, which in

Table 3. Chest deformity in asthmatic children

	With chest deformity Ratio	(n)	Without chest deformity Ratio	(n)	Trends in those with chest deformity
Family history of atopy					
Positive:negative	1.00:1	(30)	2.45:1	(38)	↓↓
Serum IgE					
Above + 1 s.d.:below + 1 s.d.	1.08:1	(25)	1.25:1	(36)	↓
Smoking in household					
Smoker:non-smoker	6.50:1	(30)	3.56:1	(41)	↑
Maternal smoking					
Smoker:non-smoker	2.00:1	(30)	0.95:1	(41)	↑↑
Pertussis immunization uptake					
Immunised:non-immunised	0.87:1	(28)	0.64:1	(36)	↑
Occupation of father					
Armed Service:civilian	1.30:1	(30)	0.46:1	(41)	↑↑
Sex distribution					
Male:female	3.29:1	(30)	1.56:1	(41)	↑↑

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most cases was manifest as a marked Harrison's sulcus and this was present in 30 (42%). More had developed chest deformity by the time of enrolment in the survey if they were male, came from Service families, had a negative family history of atopy, a serum IgE less than +1 s.d. (i.e. potentially non-atopic) and a mother or member of household who smoked (Table 3). Immunization against pertussis did not appear to confer protection against the development of chest deformity in this survey. These trends were not statistically significant. Overall a chest deformity was noted in 50% of those whose mothers smoked and 43% where a member of the household smoked.

Sex preponderance

Although there was a 66% male preponderance overall in the 86 cases (M:F 1.97:1), the preponderance in the group of potential non-atopic or 'intrinsic' asthmatics was 71% (25 of 35) compared to only 60% (21 of 35) in the potentially atopics; the male:female ratios were respectively 2.5:1 and 1.5:1. An increased male preponderance was seen also in asthmatics from Service families (2.8:1) and in those families where the mother smoked (2.1:1).

Discussion

Epidemiological studies of children with asthma and wheezy bronchitis have emphasized a high burden of illness, increasing prevalence and similar underlying mechanisms, with the need for a common approach to early diagnosis and management[8-10]. The recurrent ill health, multiple hospitalizations and early chest deformity seen in the young asthmatic children in this survey echo these findings. A most important variable, when comparing surveys of asthma, is difference in criteria used in definition[11]. Below the age of six, an exact definition of asthma is difficult to apply. The one used in this survey has proved helpful in focusing on early diagnosis and optimal management in both general practice and district paediatric unit settings.

The probability that at least two populations of young 'wheezers' might exist has been considered for some time, but it has not been clear whether these were allergic and non-allergic, atopic and 'intrinsic', or bronchitic and asthmatic[12,13]. The ventilatory response to exercise has been suggested as a good basis for separating such children. However, the poor reliability and reproducibility of bronchial lability testing in children under six years limits such a separation. Increased bronchial lability is considered to be a more likely explanation for the early male preponderance seen in young asthmatic children than atopic status which, in post-respiratory syncytial and other virus-induced wheezing, appears to be less important than it is in asthma in older children[14]. However, this explanation is not entirely convincing, and assessment of atopic status may have been inadequate in studies that have relied on family history alone[12].

Qualitative differences in the low levels of IgE at birth and in the first few years of life have permitted more accurate prediction of atopic respiratory disease, although in older children the relationship between single IgE levels and allergic symptoms remains controversial[9,13]. In Sweden, where some of this work has been carried out, the prevalence of asthma has been lower than in the UK and social conditions generally more favourable. It seems likely that some of the controversy which exists on the role of atopy has also arisen because variations in passive smoking and other important social factors have not been adequately taken into consideration in follow-up studies after virus, mycoplasma and bordetella infections, nor in bronchial lability studies on asthmatic children and their relatives[12,14]. In the most favourable social circumstances, however, atopy may more clearly be shown to predispose to asthma occurring with or as a sequel to infection[15-17].

The findings of the present Naval Hospital-based survey suggest that the majority (94%) of moderately severe young asthmatic children in whom atopic status is uncertain fall into one of three groups:

(*a*) Serum IgE > +1 s.d. above mean for age and member of household a smoker for >50% of child's first three years (atopic, passive smoker).

(*b*) Serum IgE > +1 s.d. above mean and no smoker in household (atopic, non-smoker).

(*c*) Serum IgE within +1 s.d. of mean for age and member of household a smoker for >50% of the child's first three years ('intrinsic', passive smoker).

A raised serum IgE and/or a mother who was an active smoker were noted in 84% of the 70 cases in whom IgE was measured.

It is particularly in the group of potentially non-atopic or 'intrinsic' asthmatics (Group C) that the major difference in male preponderance and parental smoking behaviour was observed. Exclusion of children with a personal history of eczema and a high local prevalence of smoking may have accounted for the high proportion of these 'intrinsic' cases (50% cf. 20% noted in other surveys)[13]. This separation into three groups may also help more satisfactorily to explain the early male preponderance in terms of the effects passive smoking might perhaps have in increasing bronchial lability and vulnerability to respiratory infections more in males than females.

The correlation of only 60.3% noted between raised serum IgE and positive family history of atopy in this survey might have been inferred from Kjellmann's findings[18] that although a family history of atopy was present in 50% of his cases with a similar atopic disease, the total incidence of atopic disease was only increased from 15% to 25% in those with a positive family history. The predictive value of serum IgE contrasts with the poor specificity of family history in providing a useful index of atopic status. In the present study, 5 children showed positive RAST tests, but serum IgE in the normal range, suggesting that there may be a significant group of mild atopics unascertained. It has been suggested that the effect of parental smoking on serum IgE levels in young children is to make the rate of rise with age more rapid and a significant difference has been shown at 36 months[19]. This would have had the opposite effect and made it more likely in the present study that atopic children would have been classified correctly.

Since the original survey undertaken by Colley *et al.*[1], there have been many others supporting their conclusions on passive smoking. The paper by Pullan *et al.*[3] in relation to respiratory syncytial virus infection is particularly clear in demonstrating the significance of maternal smoking, breast feeding, maternal care as assessed by the health visitor, and a single mother in relation to the severity of a young

Figure 4. Paternal contribution – circa 1900. (Reproduced from Pipe Dreams, 1982, with kind permission of Pavilion Books)

child's respiratory illness. These findings are supported by the larger 'National Child Development' and 'Child Health and Education in the Seventies' studies in this country and numerous surveys from other parts of the world[2,3,17,20-24]. More recently Webb *et al.*[6], in a paper on continuing symptoms three and a half years after acute bronchiolitis, showed that of all the parameters (including family history of atopy and skin tests) considered, maternal smoking was the only one which, according to their data, reached significance at the 5% level. Other factors in addition to the development of the humoral response to house-dust mite and grass pollen antigens were inferred by Rowntree *et al.*[25] in their study on the continuing incidence of asthma at five years; and in a study on children at risk from atopic disease, Cogswell *et al.*[26] also noted that the one factor found to be associated with an increased prevalence of wheeze was the presence in the household of at least one parent who smoked.

Smoking behaviour may reflect a number of other social factors such as maternal stress. Medical care utilization is also closely bound up with parental smoking habit; [redacted]. Some light may have been shed on the mechanism of this through the work of Tager *et al.*[4]. Acquired ciliary defects have been noted in nasal epithelia in children with respiratory infections, and it will be important to establish the frequency of similar defects in small children who experience significant passive smoking[27]. Cotinine estimations have established the existence of tertiary smoking and been helpful in illustrating quantitatively in the child the chemical effects of passive parental smoking[28,29].

Previous studies in Gosport have demonstrated that maternal smoking and other child care disadvantages assessed by health visitors were relevant factors in the prediction of infants at risk from sudden infant death syndrome in both the local Service and civilian populations[30]. The present survey illustrates that asthma and a family history of atopic disease are incorrectly regarded as contraindications to pertussis immunization. However, stress and adverse social factors are also suggested here and imaginative strategies will be required to counteract these[31]. The increased prevalence of parental smoking, poor uptake of pertussis immunization, and frequency of early chest deformity seen in Service families must be explained.

[redacted] Although health education programmes have not shown good immediate effect in general, a smoking cessation programme has been shown to be relatively effective in a group of sailors[32]. There remains scope for further programmes, and a clear statement is required of the necessity to avoid smoking in households two years before and at least five years after the birth of a child.

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Murray, A.B., Morrison, B.J. "Passive Smoking and the Seasonal Difference of Severity of Asthma in Children" <u>Chest</u> 94: 701-708, 1988.

ABSTRACT. To learn whether asthmatic children are affected by passive smoking, we studied 240 unselected consecutively referred asthmatic subjects, aged 7 to 17 years. To discover whether children of smokers are affected more severely during the cold, wet season, when windows are closed and children are indoors, than during the warm, dry season, when houses are well ventilated and children spend more time outdoors, we compared lung function tests recorded during the two seasons. If seen during the cold, wet season, children of smoking mothers compared with those of nonsmoking mothers had a lower FEV1% (74 vs 86, p=.00), FEV25-75 percent (56 vs 75, p=.00) and PC20 histamine (0.85 vs 1.95, p=.01). There was a highly significant correlation between the number of cigarettes the mother smoked in the house and each of these lung function test results, indicating a dose-response relationship. Those seen during the warm, dry season, by contrast, did not have lower mean spirometric test results if their mothers were smokers than if nonsmokers, and there was no correlation between the number of cigarettes the mother smoked in the house and the result of any lung function test. Our results strongly support the hypothesis that cigarette smoke from the mother aggravates her child's asthma.

Passive Smoking and the Seasonal Difference of Severity of Asthma in Children*

Andrew B. Murray, M.B.;† and Brenda J. Morrison, Ph.D.‡

To learn whether asthmatic children are affected by passive smoking, we studied 240 unselected consecutively referred asthmatic subjects, aged 7 to 17 years. To discover whether children of smokers are affected more severely during the cold, wet season, when windows are closed and children are indoors, than during the warm, dry season, when houses are well ventilated and children spend more time outdoors, we compared lung function tests recorded during the two seasons. [redacted] Those seen during the warm, dry season, by contrast, did not have lower mean spirometric test results if their mothers were smokers than if nonsmokers, and there was no correlation between the number of cigarettes the mother smoked in the house and the result of any lung function test. [redacted] (Chest 1988; 94:701-06)

Several studies have reported that children who are exposed to their parents' cigarette smoke are more likely than children of nonsmoking parents to wheeze and to have decreased spirometric test results.[1-4] [redacted] a causal relationship is not universally accepted. Doubt remains because some surveys find no difference in

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spirometric results between the children whose parents smoke and those whose parents do not smoke.[7-9]

[redacted]

The indoor level of smoke appears to be low in Arizona, even when there is a smoker in the house. In a study carried out in Tucson, Lebowitz[10] found that the indoor concentration of carbon monoxide (CO), an indicator of the smoke level, was comparable to the outdoor concentration, even though a smoker was present. When a building is well ventilated, CO from cigarette smoke is rapidly removed, but when poorly ventilated, as is the case during the heating season in colder areas, the CO concentration increases.[11] The reason for reducing the ventilation rate in cold weather is to conserve energy.[12] The consequence is that in a heated building the air is recirculated and there is an accumulation of cigarette smoke, shown by high concentration of both CO[13] and the mean mass respirable particulate (MRP), another indicator of the amount of cigarette smoke present.[14,15] Dockery and Spengler[14] found that smoke from one pack of cigarettes raised the MRP level by approximately 42 μg/cu m when the air in the building was being recirculated, but only by 18 μg/cu m when the air was not being recirculated.

If passive smoking is greater in cold, wet weather than in warm, dry weather, and if the smoke impairs lung function, we would expect children of smoking mothers in Vancouver to be more severely affected in the cold, wet season (October through May) than in the warm, dry season (June through September; Fig 1).[16] During this warm period, windows and doors are left open, a practice that rapidly changes the indoor air.[16]

[redacted] The difference in spirometric test results between children of nonsmokers and smokers reported in asthmatic subjects[17] is much greater than reported in representative groups of schoolchildren.[1-4] In such a study the mothers' smoking habits are particularly important, since children have greater

*From the Department of Paediatrics, British Columbia's Children's Hospital, and the Department of Health Care and Epidemiology, University of British Columbia, Vancouver, Canada.
†Professor of Paediatrics.
‡Associate Professor of Health Care and Epidemiology.
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Reprint requests: Dr Murray, 4480 Oak Street, Vancouver, B.C., Canada V6H 3V4

exposure to her smoke than to smoke from the father, judged by cotinine levels in the childrens saliva. The level is significantly higher if the smoker in the family is the mother rather than the father.[30]

The present study had two purposes: (1) to confirm that asthmatic children of mothers who smoke do have lower lung function test results than those of mothers who do not smoke, and (2) to find whether these children of smokers are affected more severely in the cold, wet season than in the warm, dry season.

Material and Methods

Population

The series included every child with asthma or a wheezy chest who was aged 7 to 17 years and had been referred to one of us (ABM) at the Children's Hospital in Vancouver.

There were 247 subjects. Of these, 160 were being seen for the first time, and 87 had been examined on a previous occasion; they were being reassessed at the request of their primary care physicians. For both new and old patients only the data recorded at the initial visit during the period Nov 1, 1983, to May 31, 1986, were used in the study.

Because of a long waiting list, an average period of four months elapsed between the date of referral and the day of the child's visit. As parents tend to forget instructions during such a long interval, every attempt was made to contact them by telephone 48 hours before the appointment. They were asked which medications the child was receiving and were instructed to discontinue those that might influence the bronchial challenge test.

Questionnaire

A trained interviewer put standardized questions to the patients and to the accompanying adult who, in 97 percent of cases, was a parent. All were asked how long the child had had the asthma or wheezing, whether the child had suffered from a cold or respiratory infection during the preceding two weeks,[31,32] and whether the child had received recent medication—ie, corticosteroid or antihistamine medication in the past 48 hours, theophylline in the previous 24 hours, or sodium cromoglycate or bronchodilator in the eight hours before the appointment.

Those who were being seen for the first time were also asked the following questions: whether a gas stove was used for cooking, the type of central heating in their house, whether they owned any furred household pets, and whether either of the parents or any of the siblings had ever had asthma. These items of information had also been ascertained at a previous visit for those referred for reassessment, but because conditions could have changed since the original enquiry, these old data were not used in the present study.

When the above questions had been completed, the parents or accompanying adults were asked how many cigarettes the mother and father smoked per day, both the total number and the number smoked while in the house.

The child was asked privately whether he or she smoked. Of the four who admitted to being smokers, two were children of a nonsmoking mother, and two were children of a smoking mother. Because the purpose of this study was to determine the effect of passive smoking only, these four subjects were excluded.

Forced Expiratory Spirogram

Forced expiratory maneuvers were performed until there were three in which the forced vital capacity (FVC) agreed within 5 percent. This was achieved within five efforts on all except three children, all aged seven years, who were too uncoordinated or too uncooperative to perform a forced expiratory maneuver. These children were eliminated from the series. In the remaining 240 subjects the tracing that had the greatest sum of FVC and forced expiratory volume at one second (FEV_1) was used for all measurements. The FEV_1 and the forced expiratory flow rate during the middle half of the FVC (FEF25-75) were expressed as a percentage of predicted mean for age, sex, and height.[33]

The spirogram was recorded with a Pulmonaire (Jones Medical Instrument Co) waterless spirometer that was calibrated weekly with a known volume of carbon dioxide (CO_2) discharged at a standard velocity from a calibrator instrument.

The results of the tests were analyzed and printed by a Datamatic (Jones Medical Instrument Co) computer connected to the spirometer.

Bronchial Reactivity to Histamine

A bronchial challenge test was performed on all except the following subjects: those who had taken recent medication, as defined above, those who reported a cold or respiratory infection within the preceding two weeks, or those who had an FEV_1 less than 60 percent predicted, or was below 1 L in volume.

A modification[34] of the protocol of Cockcroft et al[35] was used to find the threshold dose of histamine that would result in a fall of 20 percent in the FEV_1. After baseline spirometric measurements had been recorded the patient held a loosely fitting plastic mask to his face, inhaling an aerosol generated by air flowing at 5 L/min through a Wright nebulizer. The volume of solution aerosolized was 0.2 ml/min. Doubling concentrations of histamine acid phosphate were given until the strongest concentration, 8 mg/ml, was reached. Children whose FEV_1 did not decrease by 20 percent when this concentration was administered were deemed, for the purpose of calculating the PC_{20}, to respond to double that concentration, ie, 16 mg/ml histamine acid phosphate. There were 13 such subjects. The mothers of 12 of them were nonsmokers, and the mother of the remaining one was a smoker.

Using a standard method,[36] skin prick tests were performed on all subjects with the following materials: a negative (saline) and a positive (histamine) control solution, extracts of 1 percent *Dermatophagoides farinae* and 1 percent *D pteronyssinus* (Bencard Division of Beecham Laboratories), dog and cat hair (Hollister), and alder, birch, and mixed grass pollens (Greer Lab).

The diameter of each resulting wheal was measured. If any wheal was 2 mm greater than that of the negative control solution, the test was considered positive.

The spirometric, bronchial challenge, and skin tests were performed by a technician who was unaware of the family's smoking habits.

Season

Spirometric and bronchial challenge test results in the children seen between June and September, the warm, dry season, were compared with those recorded between October and May, the cold, wet season in Vancouver[37] (Fig 1).

From October through May there are, on average, no degree days above 18°C.[38] A "degree day" is defined as a measure of the departure for a day from some reference temperature. The reference temperature chosen for this study (18°C) is the one used for residential space heating needs.[38] Heat is required on the days when there is a negative departure from 18°C and no heat on the days when there is a positive departure. From early October until the end of May, therefore, windows and doors are closed every day to conserve heat.

Korsgaard[39] found that windows are left open for 20 hours a day in June and July but only for one hour a day in February and March. Under such circumstances the ventilation rate of the house is decreased, and the cigarette smoke generated in the house reaches high levels.[13,14,40]

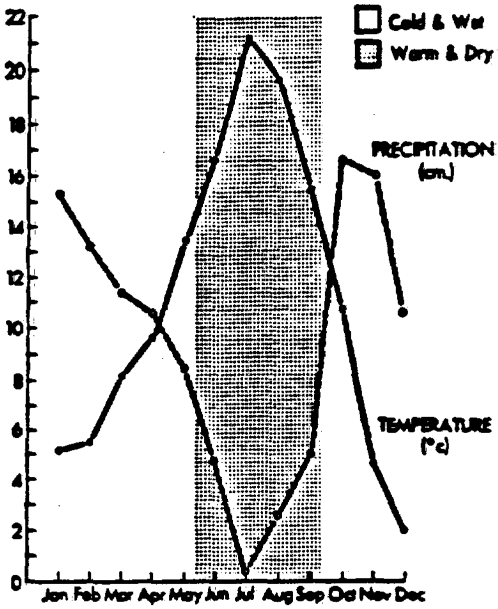

FIGURE 1. The mean monthly temperature and the mean monthly precipitation in Vancouver between November 1983 and June 1986.

From June through September there are degree days above 18°C in every month, and on these days ventilation is unrestricted, as air-conditioning is unnecessary for comfort. The mean maximum temperature in Vancouver in July and August is only 21°C.[a] Of our patients in the Vancouver area, four had air-conditioning in the parents' bedroom, but none had air-conditioning for the whole house. Two patients from cities in the interior of the province had house-wide (central) air-conditioning, the family members in these houses were all nonsmokers.

Statistical Analysis

After elimination of the four children who were themselves smokers and the three who could or would not perform an acceptable spirogram, 240 subjects remained. 183 had mothers who were nonsmokers, 56 had mothers who were smokers, and the smoking status of one mother was unknown.

For statistical analysis, differences were tested by Student's t test for those variables on a continuous scale, or a scale approximating it, and by χ^2 for those which were frequencies. Pearson's product-moment and point biserial correlation coefficients, as appropriate, were calculated to assess association. A logarithmic transformation was applied to the number of cigarettes smoked by each of the parents, the PC_{20}, and to other variables that were skewed to the right. Multiple linear regression was carried out for each season separately.

RESULTS

The two groups of children were comparable for the following features: age; male-female ratio; the duration of asthma; the occurrence, during the preceding two weeks, of a respiratory infection, a condition that may have influenced lung function test results; the taking of recent medication; and the percentage with a positive skin prick test to an inhalant allergen, an indication of atopy (Table 1). The two groups did differ,

Table 1—*Comparability of Groups*

Features	Mother Nonsmoker (n = 183)	Mother Smoker (n = 56)	p Value (2-tailed)
All patients*			
Mean age, yr	11.0±0.2	10.9±0.4	0.84
Male:Female ratio	120:63	43:13	0.16
Duration of asthma*	6.7±0.3	7.4±0.5	0.26
Recent respiratory infection*	55 (34%)	20 (38%)	0.74
Recent medication*	50 (28%)	22 (41%)	0.12
Positive skin test	158 (86%)	46 (82%)	0.57
Size of mite reaction†	3.4±0.3	1.7±0.4	0.00
New patients*	n = 117	n = 37	
Family history of asthma*	39 (42%)	9 (30%)	0.34
Heating			
Hot air	73 (62%)	20 (54%)	0.48
Wood stove*	14 (12%)	6 (17%)	0.65
Gas for cooking*	7 (6%)	3 (8%)	0.96
Household pets	50 (43%)	22 (60%)	0.22

*When the informant did not know a particular item of information, the patient was omitted from the analysis for that item. The numbers omitted were as follows:
Mother's smoking status, 1; duration of asthma, 33, recent respiratory infection, 24, recent medication, 9, family history of asthma, 32, wood stove, 4, and gas for cooking, 3.

†The size of the mite reaction was not measured in 5. Mean ± SE are presented.

however, in the mean diameter of the wheal produced by a skin prick test with house dust mite extract. Children of nonsmokers had the larger reaction, indicating either that they had a potential for being more severely affected during the cold, wet season, the period when mite-sensitive subjects in Vancouver tend to have the worse asthma,[26] or that they were more highly exposed to house dust mites,[27] or both.

In the 155 patients who were visiting the Allergy Clinic for the first time and were asked the additional questions at that visit, the children of smoking and nonsmoking mothers were also comparable for the following variables: for the percentage of houses in which airborne allergens were circulated by a forced air heating system; the percentage exposed to emissions from gas stoves, used for cooking,[28] or from wood stoves, used for heating;[29] ownership of pets to which they may have been allergic; and the proportion who had a parent or sibling with asthma (Table 1).

This newly seen group of 155 subjects were comparable in all respects to the group of 85 whose first visit to the clinic had been before the start of the study, except that the latter were older by a mean of two years and had had their asthma for one year longer (Table 2).

As in our previous study,[17] there was a highly significant association between maternal smoking and indications of increased asthma severity in the patient. Children of smoking mothers had a lower mean $FEV_1\%$ and FEF25-75%, and had a lower mean PC_{20} histamine

Table 2—Comparability Between Old and New Subjects

Features	Old (n = 85)	New (n = 155)	p Value (2-tailed)
Mean age, yr	12.0 ± 0.3	10 ± 0.2	0.00
Male:Female ratio	56:27	106:49	1.00
Duration of asthma, yr*	7.6 ± 0.5	6.5 ± 0.3	0.06
Recent respiratory infection*	32 (40%)	43 (32%)	0.27
Recent medication*	31 (37%)	42 (29%)	0.24
Positive skin test	75 (88%)	130 (84%)	0.47
Size of mite reaction†	3.0 ± 0.3	3.1 ± 0.3	0.74
FEV₁%	83 ± 1.8	83 ± 1.4	0.91
FEF25-75%	68 ± 2.7	70 ± 2.3	0.47
PC_{20} histamine‡	1.49 ± 1.2	1.82 ± 1.2	0.52

*When the informant did not know a particular item of information the patient was omitted from the analysis for that item. The numbers omitted were as follows: duration of asthma, 33, recent respiratory infection, 24, recent medication, 9.
†The size of the mite reaction was not measured in five.
‡The PC_{20} was performed on 104 subjects (geometric means are given). Mean ± SE are presented.

than did the children of nonsmoking mothers (Table 3).

There was also a significant correlation between the logarithm of the number of cigarettes the mother smoked while in the home and the FEV_1%, the FEF25-75%, and the logarithm of the PC_{20} histamine, suggesting a dose response (Table 4).

Also, as reported in our previous study,[17] there was no association between the father being a smoker or a nonsmoker and the results of any of the above-mentioned tests (Table 3), nor did the number of cigarettes he was said to smoke at home correlate with any test results (Table 4). However, in the subgroup in which the father himself had verified the number of cigarettes he smoked while in the house, there was a correlation between the logarithm of this number and the logarithm of the PC_{20} histamine ($r = -.60$, $n = 9$;

Table 3—Results of Lung Function Tests Classified by Smoking Habits of Parents

Feature	FEV_1%	FEF25-75%	PC_{20}† Geometric Mean
Mother*			
Nonsmoker (n = 183)	85 ± 1.2	73 ± 2.0	2.03 ± 1.1 (n = 78)
Smoker (n = 56)	76 ± 2.4	59 ± 3.4	0.91 ± 1.3
p value, two-tailed	0.00	0.00	0.01
Father*			
Nonsmoker (n = 166)	84 ± 1.1	71 ± 2.0	1.90 ± 1.19 (n = 70)
Smoker (n = 66)	81 ± 2.3	68 ± 3.3	1.27 ± 1.30 (n = 34)
p value, two-tailed	0.21	0.46	0.14

*Information about smoking was available for 239 mothers and 232 fathers.
†The PC_{20} was performed on all 104 children who were eligible for the test. T tests were carried out on logarithm of the PC_{20} values.

Table 4—Correlation Between Indicators of Asthma Severity and Log of the Number of Cigarettes Smoked in the House by the Parents, and Probability (p) of r = 0

Feature	Recent Bronchodilators*	FEV_1%	FEF25-75%	PC_{20}†
Mother‡				
r	0.12	−0.27	−0.27	−0.27
n	228	237	237	104
p	0.04	0.00	0.00	0.00
Father‡				
r	−0.05	−0.06	−0.03	0.00
n	223	232	232	104
p	0.22	0.17	0.33	0.07

*Information about bronchodilators was not known in 9 (point biserial correlation coefficient).
†The PC_{20} was performed on all 104 children who were eligible for the test. T tests were carried out on logarithm of the PC_{20} values.
‡The number of cigarettes smoked by the mother was available in 237 patients and by the father in 232.

$p = 0.045$). This observation suggests that cigarette smoke from the father also increases bronchial irritability in his child but that in the whole group the number of cigarettes smoked by the father was less accurately reported than the number smoked by the mother. A more accurate number for the mother is to be expected, as the history was provided by her alone in 71 percent, by the father alone in 8 percent, and by both together in 18 percent of participants. The disproportionate frequency with which the child was accompanied only by the mother suggested another reason for the good correlation between asthma severity and maternal but not paternal smoking. [redacted]

As may be expected, if passive smoking aggravates asthma, the children of smoking mothers were more severely affected in the cold, wet season than in the warm, dry season. In the cold, wet season the FEV_1% was 14 percent lower in the children of smokers than in those of nonsmokers, and the FEF25-75% was 25 percent lower (Fig 2 and 3, Table 5). These differences were statistically highly significant. In children seen during the warm, dry season, by contrast, the FEV_1% and FEF25-75% were no lower in children of smokers than in those of nonsmokers. As predicted, spirometric test results were lower if children of smokers were seen in the cold, wet season than if seen in the warm, dry season: the mean FEV_1 was 15 percent lower (t value, −2.23, two tail probability, 0.03), and the FEF25-75% was 23 percent lower (t value, −1.94, two-tail probability, 0.057) (Table 5). A smaller number of children had data for PC_{20} and for recent medication,

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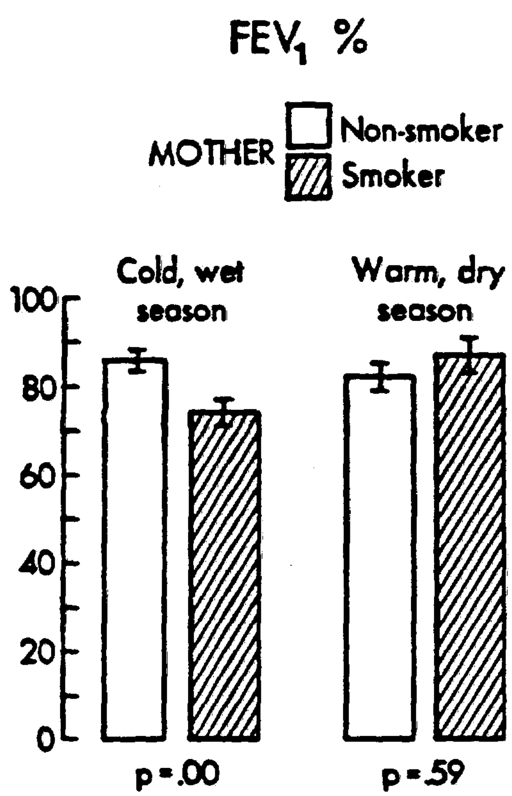

FIGURE 2. The mean FEV1% predicted in four groups of asthmatic children who were classified by their mother's smoking habits and the season in which they were seen.

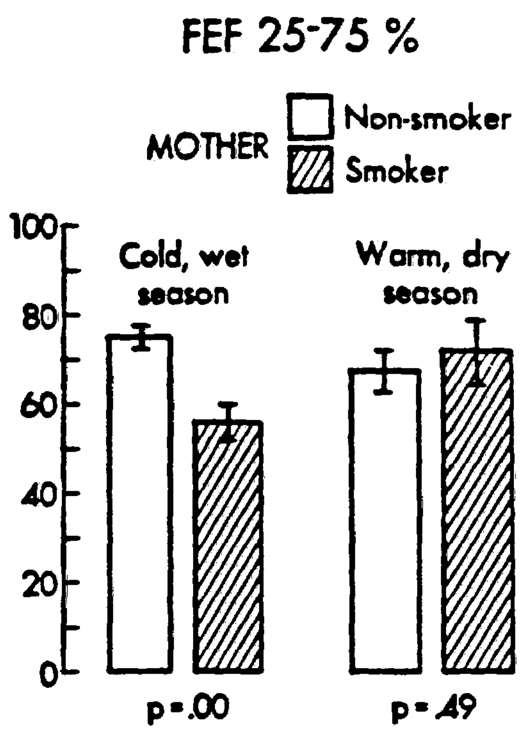

FIGURE 3. The mean FEF25-75% predicted in four groups of asthmatic children who were classified by their mother's smoking habits and the season in which they were seen.

but for these there was nonetheless a significant difference between children of smokers and nonsmokers, if seen in the cold, wet season. In this season the differences also tended to be greater than those observed in the warm, dry season (Tables 5 and 6).

As well, there was evidence of a dose-response to cigarette smoke during the cold and wet but not during the warm and dry months. In the cold, wet season there was a significant correlation between the log of the number of cigarettes the mother smoked while in the house and the likelihood of recent bronchodilator use, and also the extent of the decrease in $FEV_1\%$, in

Table 5—*The Difference Between Indicators of Asthma Severity in Children of Nonsmoking and Smoking Mothers When Measured in the Cold, Wet Season (October-May), Compared With the Warm, Dry Season (June-September)**

Season	$FEV_1\%$	FEF25-75%	Geometric Mean PC_{20}
October to May			
Mother nonsmoker (n = 141)	86 ± 1.2	75 ± 2.2	1.95 ± 1.18 (n = 61)
Mother smoker (n = 45)	74 ± 2.7	56 ± 3.8	0.85 ± 1.36 (n = 21)
t value	4.50	4.28	2.53
p (2-tail)	0.00	0.00	0.01
June to September			
Mother nonsmoker (n = 42)	82 ± 2.9	67 ± 4.5	2.37 ± 1.3 (n = 17)
Mother smoker (n = 11)	87 ± 3.6	72 ± 7.4	1.24 ± 2.1 (n = 5)
t value	−0.7	−0.55	1.02
p (2 tail)	0.49	0.59	0.32

*One subject was omitted from the analysis because the smoking status of the mother was not known. T tests were carried out on the logarithm of the PC_{20} values. Mean ± standard errors are presented.

Table 6—*The Seasonal Differences Between Nonsmoking Mothers' Children and Smoking Mothers' Children as to Whether They Had Taken Bronchodilator Medication Recently*

Season	Recent Bronchodilator Medication*			
	Yes		No	
	No.	%	No.	%
October to May†				
Mother nonsmoker	34	25	102	75
Mother smoker	19	43	25	57
June to September‡				
Mother nonsmoker	16	40	24	60
Mother smoker	3	30	7	70

*Nine subjects were omitted from the analysis because it was not known whether they had taken bronchodilator medication recently.
†χ^2 4.45 (dif = 1) p value (2-tailed) = 0.03.
‡χ^2 0.05 (dif = 1) p value (2-tailed) = 0.83.

FEF25-75%, and in the logarithm of the PC_{20} (Table 7). But during the warm, dry season there was no correlation between the number of cigarettes she smoked and any of these variables.

When multiple regression using FEV_1, FEF25-75%, and log PC_{20} as the dependent variables was carried out for each season separately, the results of the univariate analysis were confirmed. The independent variables were sex, recent respiratory infection, recent medication, positive skin test, family history of asthma, hot air heating, wood stove, gas range, presence of household pets, mother's smoking habits, father's smoking habits, and the logarithm of age, duration of asthma, and number of siblings. In the cold, wet season the number of cigarettes that the mother smoked in the house was the most strongly predictive variable for all three measures of lung function. It was the only variable significantly related to FEF25-75% and to log PC_{20}. But in the case of FEV_1 recent medication also had a significant effect. Conversely, in the warm, dry season, the number of cigarettes the mother smoked in the house had no significant relationship with any of the three measures of lung function. For FEV_1, having a gas range was the only significant predictor but, for FEF25-75%, the duration of the child's asthma and having a gas range were equally strongly correlated with the dependent variable. None of the variables was significant predictors of log PC_{20}.

Table 7—*Correlation Between Indicators of Asthma Severity When Children Are Seen in the Cold, Wet Season Compared With the Warm, Dry Season, and the Logarithm of the Number of Cigarettes Smoked in the House by the Mother, and Probability (p) of r = 0*

Season	Recent Bronchodilators*†	FEV_1%†	FEF25-75%†	PC_{20}‡
October-May				
r	0.17	−0.37	−0.35	−0.28
n	179	185	185	82
p	0.01	.00	.00	<.01
June-Sept				
r	−.08	.08	.04	−.23
n	49	52	52	22
p	.59	.58	.40	.15

*Nine subjects were omitted from the analysis because the respondent did not know whether they had received bronchodilators recently (Point Biserial correlation coefficient).
†Three subjects were omitted from this analysis because the respondent did not know how many cigarettes the mother smoked while in the home.
‡Logarithm of PC_{20} used for correlation.

Discussion

The results suggest that passive smoking in the home worsens bronchial [illegible] and [illegible] the bronchi of asthmatic children. These changes were more marked in the children of mothers who smoked compared with those of mothers who did not smoke as reported in our previous study.[7] The likelihood that it was passive smoking that caused the increased severity of asthma in the children of smokers, rather than some other difference between them and the children of nonsmokers, was strengthened by the finding that the [illegible] FEF25-75% in children of smokers were lower [illegible] in the cold, wet season, the period when children are kept indoors, when energy is [illegible] and when concentrations of smoke in the house reach high levels because of decreased ventilation rates.[illegible] During the cold, wet season there was also a significant correlation between the number of cigarettes the mother smoked in the house and the extent of the decrease in FEV_1%, FEF25-75%, and log PC_{20} (Table 7), indicating a dose-response relationship.

In the warm, dry season, by contrast, when children play outdoors and houses are well ventilated, spirometric test results were no lower in children of smokers than in those of nonsmokers, and in smokers' children the mean FEV_1 was higher in those seen in the warm, dry season than in those seen in the cold, wet months. Also, there was no correlation between the number of cigarettes the mother smoked in the house and any lung function test performed during the warm, dry season.

Although the numbers of data on bronchodilator use and PC_{20} are too small for conclusions, they indicate the same trend—that children of smokers have more severe asthma in the cold, wet season than in the warm, dry season.

In our study[17] as in several others, there was little effect attributable to cigarette smoke from the father.[2,3] This finding suggests that children inhale less smoke from their fathers' cigarettes than from their mothers', an explanation supported by the results of a study by

Jarvis and colleagues.[18] They reported that the mean cotinine level in the saliva of children is 1.95 ng/ml if only the mother smokes and 1.31 ng/ml if only the father smokes. Our study offers three possible reasons for maternal smoking being the more important. One is that fathers, on average, smoke fewer cigarettes in the house than mothers do. Another is that children are more intimately exposed to their mothers and to their cigarettes than to their fathers; the mother alone accompanied 71 percent of our subjects. Third, the number of cigarettes smoked in the house was less accurately reported for the father than for the mother; only the mother was present to provide the history in 71 percent of visits. Kolonel et al[20] found that a wife's estimate of the number of cigarettes her husband smokes is inaccurate: in only 54 percent of cases does it agree within five cigarettes per day with the husband's own estimate. It is, however, unlikely that mothers or fathers were incorrectly classified as smokers or nonsmokers. Kolonel et al[20] reported complete agreement in 95 percent of couples when the man and his wife are asked, separately, whether he is a smoker. A personal history of being a smoker or nonsmoker has also been shown to be accurate, using expired carbon monoxide and serum thiocyanate levels as markers of smoking,[21] nor is it likely that a significant number of the children were incorrectly classified as nonsmokers.

To attribute the results of our study to an error of classification, one would have to postulate that nonsmokers' children are more honest than are smokers' children, and that smokers' children who are seen in the warm, dry season are more honest than are smokers' children seen in the cold, wet season. A more likely explanation for the low prevalence of active smokers in our patient population is that they are aware that cigarette smoke aggravates their asthma, and so they do not smoke. In support of this hypothesis is the finding by O'Connor et al[22] that none of the asthmatic children in their survey was a smoker. When asked privately whether they are smokers, children usually give an honest answer. Pedersen et al[23] measured CO in expired air and found that 5.5 percent, at most, gave false information. Neither is it likely that a difference in social class or referral pattern accounted for the more severe asthma found in children of smoking mothers. Social class is usually determined by the father's occupation,[24] yet we found no relationship between the father's smoking habits and his child's spirometric test results, whereas there was a highly significant relationship between these results and the mother's smoking habits. If smoking mothers are more reluctant to take their children to a pediatric allergist than nonsmoking mothers, one would expect children of smokers to have had asthma for a greater number of years. This was not the case. There was no significant difference between the two groups in the duration of the child's asthma.

Although there was no association between the fathers' smoking and the results of the children's spirometric tests, there was nonetheless some evidence that his smoke might be influencing bronchial irritability in the child. There was a significant correlation between the logarithm of the child's PC_{20} and the logarithm of the number of cigarettes the father himself said he smoked while in the house.

Greater exposure to other pollutants, such as combustion products from wood-burning stoves[25] or gas for cooking,[26] did not seem to account for the worsened asthma in the children of smoking mothers. Similar proportions in both groups used wood stoves for heating and gas stoves for cooking. Nor was there a significant difference between the two groups in ownership of pets, which might aggravate asthma in susceptible subjects, nor in the use of forced-air heating systems, which might circulate allergens.

Our demonstration that passive smoking affects asthma significantly only during the cold, wet season is consistent with results obtained in surveys of representative samples of schoolchildren in different regions of North America and in Britain. Those surveyed in Arizona, a warm, dry part of the United States,[7,8] and those surveyed during the summer in Britain[28] showed no significant difference in spirometric test results between children of smokers and nonsmokers. Surveys conducted in areas with cold winters, by contrast, usually reveal significant differences between the two groups.[1-6] But even in these areas, the difference in spirometric values between children of smoking mothers and nonsmoking mothers is small, not exceeding 5 percent, and is considerably smaller than in our study on asthmatic subjects, suggesting that representative groups of schoolchildren are less severely affected by maternal smoking than are asthmatic children.

Our finding that bronchial responsiveness is greater in asthmatic children of mothers who smoke than in those of mothers who do not smoke is also consistent with previously published articles. We reported earlier an increased bronchial responsiveness in children of smoking mothers in a group of 94 asthmatic children;[17] such an increase was also subsequently noted in a community-based sample of 21 asthmatic children by O'Connor et al.[22]

Passive smoking is likely to be the cause of the greater bronchial irritability and the increased bronchial obstruction which we find in asthmatic children of smoking mothers compared with those of nonsmoking mothers. Although children in the two groups are comparable in other respects and have similar indications of asthma severity during the warm, dry season when their houses are well ventilated, children of

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smoking mothers have pulmonary function that is significantly poorer during the cold, wet season when houses are closed up, when indoor cigarette smoke reaches its highest level, and when the children spend more time in the house.

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Somerville, S.M., Rona, R.J., Chinn, S. "Passive smoking and respiratory conditions in primary school children" Journal of Epidemiology and Community Health 42: 105-110, 1988.

ABSTRACT. The effect of passive smoking on respiratory symptoms of children aged 5 to 11 years was investigated in over 4000 English children and nearly 800 Scottish children participating in the National Study of Health and Growth in 1982. After adjusting for associations of respiratory symptoms with age, sex, and a number of potentially confounding variables, significant associations were found of wheeze, both occasional and persistent, day or night cough, and bronchitis attacks with number of cigarettes smoked by parents at home for English children and for occasional wheeze in Scottish children. Asthma attacks and cough first thing in the morning showed positive but not statistically significant associations in English children. The presence of at least one condition was statistically significant in both English and Scottish children. The largest relative risk for exposure to 20 cigarettes a day compared to no exposure was 1.60 for persistent wheeze in English children (95% confidence interval 1.17-2.18).

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Passive smoking and respiratory conditions in primary school children

SHEENA M SOMERVILLE, ROBERTO J RONA, AND SUSAN CHINN

From the Department of Community Medicine, United Medical and Dental Schools of Guy's and St Thomas's Hospitals, St Thomas's Campus, London SE1 7EH

SUMMARY The effect of passive smoking on respiratory symptoms of children aged 5 to 11 years was investigated in over 4000 English children and nearly 800 Scottish children participating in the National Study of Health and Growth in 1982. [redacted] Asthma attacks and cough first thing in the morning showed positive but not statistically significant associations in English children. The presence of at least one condition was statistically significant in both English and Scottish children. [redacted]

Among the harmful effects postulated for passive smoking is a possible association between parental smoking and respiratory conditions in children, which has been investigated in a large number of studies. A review article[1] concluded that the studies were consistent in suggesting increased infections in children under 1 year of age but inconsistent in older children. [redacted]

The studies on older children have varied in the symptoms studied, in the age range of the children, in the proportion of parents who smoked, and in the potentially confounding variables that have been taken into account. A report of a workshop on the effect of passive smoking on children[2] listed nine groups of such variables that it is desirable to take into account. No study has included all of these, and most included only a few variables in one or two of the listed groups. This can be attributed largely to the fact that few[2] of the studies were designed to investigate passive smoking effects, and were opportune analyses on data collected mainly to investigate the relations in children between symptoms and lung function and a variety of environmental factors.

Of even more importance to the detection of a dose-response relation the studies have differed markedly in size and in the measure of passive smoking. The most usual measure was the number of parents smoking, providing lower power to detect a dose-response relation than a measure of the amount smoked. A recent review[3] reported only three studies of young children in which the measure of passive smoking was cigarettes smoked per day, and just one study of older children.

The National Study of Health and Growth, an on-going surveillance study of the health and growth of primary school children in England and Scotland, was also not designed to investigate passive smoking effects. Data on the number of smokers of five or more cigarettes a day in the child's home were collected in 1977 as a confounding variable in a study of the relation of respiratory illness and outdoor air pollution.[4] These data also suggested a negative relation of child's height to number of smokers in the home after adjusting for birthweight.[5] In order to study this association further, data on the number of cigarettes smoked at home by each parent, and by the mother during pregnancy, were collected in 1982.[6] No data on lung function were obtained.

Further examination of the 1977 data on English and Scottish children showed a number of statistically significant positive associations of respiratory symptoms with the number of smokers. Given the reasonable sample size, the availability of data for a

Table 1 *Number of children for whom data on each respiratory condition were obtained and the prevalence (%) of each condition, by sex and country*

	England				Scotland			
	Boys		Girls		Boys		Girls	
Respiratory condition	No	Prevalence %	No	Prevalence %	No	Prevalence %	No	Prevalence %
Chest EVER sound wheezy or whistling	3063	12·6	2870	9·5	572	13·1	563	6·9
Chest wheezy or whistling on MOST days or nights	3046	3·2	2858	2·6	569	4·4	564	2·8
In the last 12 months had:								
Bronchitis attack(s)	3030	4·0	2852	2·7	570	3·5	565	2·1
Asthma attack(s)	3060	4·2	2862	2·8	568	2·3	567	2·1
Usually coughs first thing in the morning	3048	4·2	2851	4·5	569	5·1	558	5·0
Usually coughs during the day or at night	3036	8·3	2858	7·8	568	11·1	560	8·4

number of potentially confounding variables, and the almost unique data on amount of smoking in the home, it was decided to investigate the dose-response relation of symptoms to passive smoking, using the 1982 data, in children aged 5 to 11 years.

Methods

In 1982 children took part in the study in 22 areas in England and five in Scotland. Data on the child's respiratory symptoms, parental smoking, and family background were obtained from a self-administered questionnaire completed by the child's mother. Triceps skinfold thickness was measured as described elsewhere[7] and was included in the analysis as previously[8] a relation had been shown between respiratory symptoms and this measure of obesity.

Each of six respiratory symptoms or illnesses, given in table 1, was analysed as a dichotomous, ie, present or absent, dependent variable using logistic regression. Any child with a missing value was excluded from the analysis of that symptom. The number of cigarettes smoked per day at home by the mother and father in total, the passive smoking component, and the number of cigarettes smoked per day by the mother during pregnancy with the child were each included as a quantitative variable. Two groups of potentially confounding variables were included in the regression analyses, those treated as quantitative variables and those that were categorical variables. The former group consisted of the child's age, birthweight, triceps skinfold thickness expressed as a standard deviation score,[7] mother's age, and number of siblings. The categorical variables were: child's sex; father's social class, in four groups as non-manual, skilled manual, semi-skilled or unskilled manual, or other; father employed, unemployed or not known; child in one-parent family, two-parent, or not known; presence or absence of household overcrowding, defined as a ratio of people in the household to number of rooms of at least 1·25; mother's education as highest full-time level in seven groups, none or primary only, secondary or comprehensive school, grammar, technical or commercial college, university, other, or not known. Except as stated missing data excluded a child from the analysis.

Analyses were carried out with all these as independent variables and also with just parental smoking, age, and sex as the independent variables, for England and Scotland separately, and for the two countries combined. Analyses were also carried out for each sex separately and, using the fully adjusted model, with the dependent variable as presence of at least one of the respiratory conditions.

Results

In 1982 there were 8118 children eligible to take part in the study; a questionnaire was returned for 87·8% of these children.

Table 2 *Distribution of cigarettes smoked per day by parents at home in England and Scotland*

No. of cigarettes (total smoked by father and mother)	% of parents	
	England	Scotland
0	57·9	39·9
≤4	3·4	3·0
5–14	16·9	19·9
15–24	12·4	19·7
25–34	5·2	9·2
≥35	4·2	8·4
No of children whose parents are included in the table	5169 (100%)	928 (100%)

Table 3 *Results of logistic regression analyses for England showing the association between respiratory symptoms and passive smoking[#] from the fully adjusted model*

Respiratory symptom	*Regression coefficient ± standard error*		
	Boys (N = 2181 to 2246)	*Girls (N = 2074 to 2128)*	*All children (N = 4255 to 4371)*
Chest EVER sound wheezy or whistling	0·008 ± 0·007	0·014[+] ± 0·008	0·011[*] ± 0·005
Chest wheezy or whistling MOST days or nights	0·037[**] ± 0·011	0·010 ± 0·013	0·024[**] ± 0·008
In the last 12 months had:			
Bronchitis attack(s)	0·004 ± 0·012	0·033[*] ± 0·013	0·018[*] ± 0·008
Asthma attack(s)	−0·005 ± 0·012	0·026[+] ± 0·013	0·009 ± 0·009
Usually coughs first thing in the morning	−0·002 ± 0·012	0·022[*] ± 0·011	0·012 ± 0·008
Usually coughs during the day or at night	0·007 ± 0·008	0·020[*] ± 0·008	0·013[*] ± 0·006
At least one condition	0·008 ± 0·006	0·011 ± 0·007	0·009[*] ± 0·005

[+] $p<0·1$ [*] $p<0·05$ [**] $p<0·01$
[#] parental smoking defined as the total number of cigarettes smoked at home by mother and father together

PREVALENCE OF RESPIRATORY CONDITIONS
Table 1 shows the number of children for whom data were obtained on each respiratory condition, which varied from 86·4% to 87·1% of the total eligible, and the percentage with each condition, by sex and country. The prevalence of each condition was greater in boys than in girls but differed little between England and Scotland.

DISTRIBUTION OF PASSIVE SMOKING
Data on parental smoking were available for 75·1% of children. The distributions of the number of cigarettes smoked per day by the parents at home are given in table 2 for children in England and Scotland. Smoking by parents was more prevalent in Scotland than in England.

RELATION OF RESPIRATORY CONDITIONS TO PASSIVE SMOKING
After exclusions for missing data, primarily in respiratory symptoms or parental smoking, the number of children available ranged from 4337 (63·4%) to 4371 (63·9%) for England and from 766 (60·90%) to 771 (61·3%) for Scotland. Table 3 shows the relation of six respiratory conditions to passive smoking for English children as estimated from the logistic regression analysis, adjusted for all the potentially confounding variables listed above. For all children parental smoking was most strongly positively associated with chest wheezy or whistling on most days or nights ($p<0·01$) and also significantly associated ($p<0·05$) with usually coughs during the day or night, chest ever sounds wheezy or whistling, and bronchitis attacks in the last 12 months. The relation was positive for the other two conditions. Although results appeared to show some differences between boys and girls, no significant difference, as assessed from an interaction term in the model, was found in the relation of passive smoking [redacted] and a non-significant negative relation in boys. [redacted]

Results are given for England and Scotland separately as the relation of 'chest ever wheezy' and 'wheeze most days or nights' to passive smoking was found to differ significantly between the two countries ($p<0·05$). 'Wheeze most days or nights' showed a relation to passive smoking only in England, whereas 'chest ever wheezy' showed a stronger relation to passive smoking in Scottish children than in English, of similar size to that for persistent wheeze in English children.

EFFECTS OF ADJUSTMENT FOR CONFOUNDING VARIABLES
Table 4 shows the relation between passive smoking and each respiratory condition adjusted only for age for boys and girls separately, and for age and sex for all English children. Comparison with table 3 shows that in most cases adjustment for the potentially confounding variables generally increased the standard errors so there was a reduction in statistical significance, the notable exceptions being 'chest wheezy or whistling most days or nights' in boys, and bronchitis attacks in girls for which the regression coefficient increased considerably on adjustment. For

Table 4 *Results of logistic regression analyses for England showing the association between respiratory symptoms and parental[#] smoking for the model adjusted only for age (and sex for all children)*

Respiratory symptom	Regression coefficient ± standard error		
	Boys (N = 2181 to 2246)	Girls (N = 2074 to 2128)	All children (N = 4255 to 4371)
Chest EVER sound wheezy or whistling	−0·002 ± 0·006	0·013* ± 0·006	0·005 ± 0·004
Chest wheezy or whistling MOST days or nights	0·023* ± 0·009	0·033** ± 0·009	0·028*** ± 0·007
In the last 12 months had:			
Bronchitis attack(s)	−0·002 ± 0·010	0·022* ± 0·010	0·008 ± 0·007
Asthma attack(s)	−0·014 ± 0·010	0·018+ ± 0·010	0·000 ± 0·007
Usually coughs first thing in the morning	0·001 ± 0·010	0·021* ± 0·008	0·012+ ± 0·006
Usually coughs during the day or at night	0·015* ± 0·006	0·026*** ± 0·006	0·021*** ± 0·004
At least one condition	0·005 ± 0·005	0·012* ± 0·006	0·008* ± 0·004

N = the range of the number of children in the six analyses
+ $p<0·1$ * $p<0·05$ ** $p<0·01$ *** $p<0·001$
[#] See footnote to Table 3

Table 5 *Estimates of prevalence (%) of respiratory symptoms and relative risk for children* of parents smoking no cigarettes, 10 and 20 cigarettes at home per day, based on the fully adjusted model for all children*

Respiratory condition	Prevalence % (relative risk compared to non-smoking parents) — Cigarettes smoked at home by parents		
	0	10	20
Chest wheezy or whistling on MOST days or nights	2·8	3·5 (1·27)	4·5 (1·60)
Bronchitis attack(s) in the last 12 months	3·9	4·7 (1·18)	5·5 (1·40)
Usually coughs during the day or night	7·7	8·7 (1·13)	9·8 (1·27)
At least one condition	17·9	19·3 (1·08)	20·8 (1·16)

* Given for boys aged 8 years, with no siblings, in a two parent family, father employed and social class IIIB, mother's smoking in pregnancy 0, home not overcrowded, mother aged 32 and educated at a secondary or comprehensive school, triceps skinfold standard deviation score 0, birthweight 3000 g

all Scottish children, adjusting only for age and sex, significant associations were found between passive smoking and chest ever wheezy ($p<0·01$), usually coughs during the day or night ($p<0·05$), and prevalence of at least one condition ($p<0·01$).

ESTIMATES OF RELATIVE RISK

Table 5 gives examples of prevalence of respiratory conditions and relative risk (in parentheses) estimated from the regression coefficients in the fully adjusted model for the three conditions showing the largest associations with passive smoking in all English children. Compared with children whose parents do not smoke the relative risks were around 1·2 for children whose parents smoke 10 cigarettes a day in total at home and from 1·3 to 1·6 for those whose parents smoke 20 a day. They are of necessity given for fixed values of the other independent variables but would not differ markedly for different values of these variables. The relative risk of at least one condition is however only just significantly different from 1·0 at the 5% level, but shows the estimated increase in the percentage of children suffering some respiratory symptom at the given levels of parental smoking.

Discussion

A number of statistically significant positive associations were found between respiratory conditions in children and number of cigarettes smoked per day at home by their parents, but not consistently for all symptoms or in both countries. The result also differed to some extent from those found in the 1977 data, in which the passive smoking variable, number of smokers of at least five cigarettes a day in the home, was significantly associated ($p<0·05$) with all six conditions except bronchitis in the last 12 months. The analyses of the two years' data differed in the confounding variables taken into account, the use of gas for cooking and population density being

included in the 1977 analysis, but not maternal smoking in pregnancy or mother's education or age. They were similar in the age range of the children, in sample size, and in the wording of the questions about respiratory conditions.

Inevitably, other studies have differed in the symptoms or illnesses studied and in the exact questions asked. However the largest study with a similar age range,[9] in which 10 106 children aged 6 to 10 years were involved, found highly significant associations ($p < 0{\cdot}001$) between cough for three months or more of the previous year and wheeze most days or nights with maternal smoking, and a less significant association ($p < 0{\cdot}01$) of bronchitis with maternal smoking, broadly in line with our findings.

Other studies have also found significant positive associations between persistent cough and parental smoking,[10–12] and, although not statistically significant, a relative risk of 4·9 for persistent wheeze was found for children exposed to a smoker at home compared to those never exposed in a study of 626 children under 15 years.[12]

The only other study[13] to include 'cough first thing in the morning' found a positive association ($p < 0{\cdot}05$) in 12 year old girls after allowing for the child's own smoking. Many studies of passive smoking have included non-persistent wheeze, with various definitions, and some asthma or bronchitis. About half of those obtained significant positive associations, and the rest non-significant associations. However, few studies have included all four symptoms of wheeze, cough, asthma, and bronchitis. Apart from the question of prime importance being whether passive smoking causes any harmful effect to children of primary school age, the nature of the effect being a secondary consideration, the symptoms are not manifestations of distinct diseases. Analysis of single symptoms may fail to detect a real increase in the prevalence of a condition. In particular, an effect of passive smoking increasing symptoms of asthma may be missed if only a question about asthma is included due to underdiagnosis in many children with wheeze[14 15] and the fact that cough may be the only presenting symptom.[16]

No data were available on active smoking by the children as the questionnaire was completed by a parent. However, even in the oldest age group and on the assumption that smoking by the child is strongly associated with parental smoking, the prevalence of active smoking would be too small to account for the differences in prevalence of respiratory symptoms. Dobbs and Marsh[17] reported a prevalence of regular smoking, defined as 'at least one cigarette a week', of 1% and 0% in first year secondary school boys and girls respectively, in England in 1982, and 5% and 3% in Scotland. Of the groups of other confounding variables that have been suggested[2] that are relevant to children's symptoms as reported by the mother, those of other indoor pollutants are probably the most important ones not included in the analysis of the 1982 data. In the analysis of 1977 data the use of gas for cooking, an important source of nitrogen dioxide in the home,[18] did not eliminate positive associations of respiratory symptoms with passive smoking.

Parental symptoms are on the list of potentially confounding variables,[2] and there is no doubt that a child's symptoms show a relation to these.[9 10 12 19] However, as many of the symptoms of smokers will be a result of their smoking, adjustment for parental symptoms could remove a real effect of parental smoking on a child's health.[20] Of the few studies in which the adjustment had been made the largest[9 20] still found positive associations between child's cough and wheeze and maternal smoking in over 10 000 6–10 year old children. Lebowitz,[12] in a much smaller study, found statistical significance of an association removed by the adjustment. Schenker *et al*[19] found a positive association between chest illness on at least three days in the last year which persisted on adjustment for parental respiratory disease, but found no association before or after adjustment in chronic cough, phlegm or wheeze in 4000 children aged 5 to 14.

Studies have varied in the prevalence of respiratory conditions and in the percentage of parents smoking. While low values of either may lead to statistically insignificant results in the presence of a real effect, the most important variation in the studies has been in sample size. The majority of studies provide no information on the amount smoked by parents. For children of two parents who smoke the estimated relative risk of the respiratory conditions studied was less than two compared to children of non-smoking parents in almost all studies.[3] The conclusion that emerges is that if there is a real effect of passive smoking on the respiratory health of children aged 5 to 11 years, then it is a small one, and a large study is required for a high probability of its detection. Although results for the smaller sample of Scottish children were not significantly different from those for English children, except for wheeze, a significant relation was found only for 'chest ever wheezy' and at least one condition. For English children the largest relative risk was for persistent wheeze, of 1·60 in children whose parents smoked a total of 20 cigarettes a day (95% confidence interval 1·17–2·18), and 1·16 (1·00–1·34) for any symptom. The USA six cities study[9] found a relative risk of 1·3 for persistent wheeze in 6 to 10 year old children whose mothers smoke 20 cigarettes a day [illegible]. As the association is probably less strong than that for children under 1 year it is to be expected that secondary school children would show a weaker, or no

association of symptoms with passive smoking. We have therefore confined consideration of the literature to studies including broadly similar age groups. All four studies[9,13,21,22] that we have identified with an analysis of data for 6000 or more children in a similar age range to those in our 1982 English sample have shown at least one significant positive association with passive smoking. The two largest[21,22] also showed a dose-response relation. Our data have supported the hypothesis of an effect of parental smoking on children of this age. Scepticism could be removed further only by a study of several symptoms in at least 6000 children, including all potentially confounding variables as recommended,[2] with a quantitative measure of passive smoking by the child.

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ABSTRACT. The relations among parental reports of respiratory symptoms, bronchospasm measured after exercise, and the presence of visible fungal mould in the home was assessed in a population sample of 7 year old children (n=873). Wheeze in the past year was the symptom most closely associated with reported dampness and particularly with mould. The unadjusted odds ratio relating mould and wheeze was 3.70 (95% confidence interval 2.22 to 6.15), and after adjustment for housing tenure, number of people per room, number of smokers in the household, and gas cooking this remained highly significant (odds ratio 3.00 (1.72 to 5.25)). The reduction in forced expiratory volume in one second after six minutes of free running was used to validate reporting of wheeze. At all levels of measured bronchial lability wheeze was reported more commonly in the children from homes with mould. There was no significant difference in the degree of bronchospasm measured among children from homes with and without mould.

Awareness of dampness or mould in the home may be a determinant of parental reporting of symptoms and may account for much of the observed association between mould and respiratory symptoms.

Damp housing and childhood asthma: validation of reporting of symptoms

D P Strachan

Abstract

The relations among parental reports of respiratory symptoms, bronchospasm measured after exercise, and the presence of visible fungal mould in the home was assessed in a population sample of 7 year old children (n=873). Wheeze in the past year was the symptom most closely associated with reported dampness and particularly with mould. The unadjusted odds ratio relating mould and wheeze was 3·70 (95% confidence interval 2·22 to 6·15), and after adjustment for housing tenure, number of people per room, number of smokers in the household, and gas cooking this remained highly significant (odds ratio 3·00 (1·72 to 5·25)). The reduction in forced expiratory volume in one second after six minutes of free running was used to validate reporting of wheeze. At all levels of measured bronchial lability wheeze was reported more commonly in the children from homes with mould. There was no significant difference in the degree of bronchospasm measured among children from homes with and without mould.

Awareness of dampness or mould in the home may be a determinant of parental reporting of symptoms and may account for much of the observed association between mould and respiratory symptoms.

Introduction

In industrialised countries people spend much of their life indoors, and interest in the public health effects of the indoor environment is growing.[1] Children are particularly appropriate for investigation of the influence of environmental variables on respiratory disease because active smoking and occupational variables are excluded. Much attention has focused on the potential hazards from passive exposure to tobacco smoke[2-4] and from nitrogen dioxide produced by gas cookers, unvented gas appliances, and paraffin heaters.[5-7]

A common cause of complaint to landlords and local authorities is condensation of moisture from humid indoor air on to cold surfaces, which forms unsightly damp patches and promotes the growth of fungal moulds.[8,9] Surveys in Scotland and England have suggested that between one quarter and one third of homes may be affected to some degree.[10,11] Poor quality housing in general and dampness in particular are widely believed to be detrimental to respiratory health.[12,13] Allergic reactions to house dust mites, which thrive in damp homes,[14,15] or to the airborne spores of fungal moulds[16] are plausible mechanisms for a causal link between damp conditions and symptoms related to asthma.

Few epidemiological studies have investigated this association, but two small studies in north west Edinburgh showed a positive relation between reported dampness and mould and respiratory symptoms in children.[11,17] Similar findings have been reported in adults.[18,19] Dampness (assessed independently by environmental health officers) and high ambient humidity were found more commonly in the homes of children with respiratory symptoms,[11,19] which indicated that reporting of housing conditions was not substantially biased by the presence of disease in the child. On the other hand, when consultations with general practitioners for respiratory complaints were used to validate reporting of symptoms there was no association with reported dampness or mould.[17] This raised the possibility that symptoms were reported differently according to parents' perception of their home environment.

My study was designed to investigate damp, mouldy housing as a determinant of childhood asthma in a representative sample of the general population and to evaluate the role of differential reporting of symptoms in any association. In view of the limitations of general practice records for this purpose the symptoms were validated by physiological tests to detect abnormal reactivity of the airways.[20]

Subjects and methods

A random sample of one in three primary schools within the Edinburgh city boundary was obtained. The parents of all children in their third primary school year (age 6½-7½ years) were contacted by post in November 1986. A questionnaire asked about respiratory symptoms experienced by the child in the past year, including wheeze (defined as breathing that makes a high pitched whistling sound), a tendency for colds to go to the chest, sore throat, pain or discharge in the ear, and hay fever or frequent sneezing attacks. Parents were also asked how many nights the child had been kept awake by coughing during the previous month and how many days in the month the child had been troubled by daytime cough or by a blocked or running nose. Information was sought about conditions in the home, particularly the number of cigarette smokers in the household, the fuels used for heating and cooking, the formation of condensation or damp patches on walls, and the presence of mould or fungus.

Consent was requested for medical tests on the child at school, and the study received ethical approval from Lothian Health Board and Lothian Regional Council Education Department. Ventilatory function was measured with a pneumotachograph (Compact; Vitalograph, Buckingham), and spirometry was performed with the child standing and without nose clips; I supervised all measurements using the protocol of the American Thoracic Society.[21] Measurements were taken before and five and 10 minutes after six minutes of free running in a corridor or classroom; the best of three recordings on each occasion was used. An index of bronchial lability induced by exercise was calculated as the minimum of the two measurements of forced expiratory volume in one second taken after exercise divided by the forced expiratory volume in one

Department of Community Medicine, University of Edinburgh, Edinburgh EH8 9AG
D P Strachan, MRCP, *Wellcome research training fellow in clinical epidemiology*

Correspondence to: Department of Epidemiology, London School of Hygiene and Tropical Medicine, London WC1E 7HT.

second obtained before exercise. Tests were performed at least six hours after a dose of inhaled bronchodilator. Eleven children were taking inhaled steroids or oral drugs for asthma; their results were analysed separately.

Routine statistical analysis was performed with the Statistical Analysis System.[22] To explore in more detail the relations between symptoms and housing conditions and between mould, wheeze, and bronchial lability multiple logistic regression models were analysed with the generalised linear interactive modelling system.[23]

Results

The parents of 1095 children received a questionnaire, and usable replies were obtained for 1012. Information on respiratory symptoms and housing conditions was available for 926-1004, depending on the detail required. Parental consent for clinical testing was obtained for 941 children. Twenty of these were included in pilot studies, and a further 20 moved to a different school before testing. Of the remaining 901 children, 892 were examined and 881 performed a satisfactory exercise test.

Complete information on dampness, mould, wheeze, and bronchial lability was available for 873 children (80% of the original sample, 97% of those eligible for testing). The prevalences of wheeze in the past year (12·7%; 111/873) and exposure to mould in the home (9·3%; 81/873) were somewhat higher in this group than among those with incomplete information (10·0% (13/130) and 6·3% (8/127), respectively).

Table I relates respiratory symptoms to various aspects of the home environment. The prevalences of wheeze and chesty colds were higher by a factor of between two and three among the children from homes reported to be affected by damp patches on walls or by mould; the higher prevalences among children sleeping in damp or mouldy bedrooms might be interpreted as evidence of a dose-response relation. Cough at night and during the daytime was significantly more common among children sleeping in damp bedrooms ($p<0·001$ and $p<0·05$, respectively), and a smaller excess was observed in children sleeping in bedrooms affected by mould. Mould in the child's bedroom was significantly related to frequent trouble with a blocked or running nose ($p<0·05$). [redacted] These relations in part reflected differences in the use of fuels by owner occupiers and tenants of rented housing. The pattern of association between dampness and hay fever was inconsistent; the difference in prevalence between all damp homes considered together and homes not affected was negligible ($\chi^2=0·54$, df=1).

The association between damp, mouldy housing and wheeze was remarkable in view of the lack of a relation of wheeze to other environmental factors in the home. Compared with rented homes, owner occupied homes were less likely to be affected by dampness (83% (58/700) v 29·7% (89/300)) or mould (4·9% (34/700) v 18·3% (55/300)); this accounted for the difference in the prevalence of wheeze by housing tenure. In homes not affected by damp or mould the prevalence of wheeze was similar in the rented sector (11·1%; 23/207) and in owner occupied homes (10·6%; 67/631). [redacted]

Possible confounding effects were investigated by multiple logistic regression models with wheeze in the past year as the outcome variable. The unadjusted odds ratio for mould anywhere in the home was 3·70 (95% confidence interval 2·22 to 6·15; $\chi^2=27·7$, df=1). In a model that included housing tenure, number of smokers in the household, number of people per room, and gas cooking the odds ratio for mould was 3·00 (1·72 to 5·25; $\chi^2=15·2$, df=1). The effect of mould was independent of housing tenure (χ^2 for interaction term=0·41, df=1). There was a close correlation

TABLE I—*Prevalence (%) of respiratory symptoms related to home environment. Numbers of children are given in parentheses*

	Wheeze (during past year)	Chesty colds (during past year)	Cough at night (≥3 nights in past month)	Cough during day (≥3 days in past month)	Running nose (≥7 days in past month)	Hay fever (during past year)	Ear trouble (during past year)	Sore throat (during past year)
Tenure:								
Owners	10·7 (75/702)	13·5 (93/690)	7·8 (54/692)	13·2 (91/689)	12·5 (85/682)	10·8 (74/684)	24·1 (165/685)	50·4 (348/691)
Renting	16·3* (49/301)	27·4*** (80/292)	22·5*** (66/293)	22·0*** (63/286)	19·0* (54/284)	8·5 (24/281)	24·3 (70/288)	56·3 (166/295)
People per room:								
<1·0	11·5 (39/338)	15·6 (52/334)	8·0 (27/336)	13·4 (45/335)	12·4 (41/331)	9·6 (32/332)	26·3 (88/334)	51·2 (172/336)
1-1·5	13·3 (66/496)	17·2 (84/487)	13·0* (63/486)	17·1 (83/484)	16·1 (77/477)	10·5 (50/478)	22·1 (106/480)	51·9 (252/486)
>1·5	11·1 (14/126)	25·0* (31/124)	18·7** (23/123)	15·4 (18/117)	13·6 (16/118)	10·8 (13/120)	23·0 (28/122)	54·4 (68/125)
Smokers in household:								
0	12·1 (64/530)	14·8 (77/519)	9·0 (47/523)	13·9 (72/519)	10·9 (56/513)	10·2 (53/518)	23·5 (122/519)	51·1 (268/524)
1	12·1 (37/307)	18·4 (55/299)	14·0* (42/301)	16·5 (49/297)	17·2* (51/297)	10·3 (30/290)	25·3 (75/296)	52·5 (158/301)
≥2	13·4 (22/164)	25·3** (41/162)	19·5*** (31/159)	20·4 (32/157)	20·1** (31/154)	9·7 (15/155)	24·4 (38/156)	55·3 (88/159)
Gas cooker:								
No	13·0 (55/422)	21·0 (87/414)	13·5 (56/415)	15·3 (63/411)	14·7 (59/402)	10·6 (43/405)	21·9 (89/407)	53·1 (220/414)
Yes	11·7 (68/579)	15·2* (86/566)	11·2 (64/569)	16·0 (90/563)	14·2 (80/564)	9·7 (54/558)	25·9 (146/564)	51·4 (293/570)
Bottled gas stove:								
No	12·4 (114/920)	16·8 (151/901)	11·9 (108/905)	15·8 (141/895)	14·5 (129/887)	10·2 (91/889)	24·0 (214/892)	51·7 (467/904)
Yes	12·8 (10/78)	27·6* (21/76)	13·2 (10/76)	14·3 (11/77)	10·8 (8/74)	9·7 (7/72)	23·7 (18/76)	55·8 (43/77)
Paraffin heater:								
No	12·4 (121/974)	17·6 (168/953)	11·8 (113/958)	15·6 (148/949)	14·0 (131/939)	10·4 (97/937)	24·1 (228/945)	52·0 (498/958)
Yes	12·5 (3/24)	16·7 (4/24)	21·7 (5/23)	17·4 (4/23)	27·3 (6/22)	4·2 (1/24)	17·4 (4/23)	52·2 (12/23)
Coal fire:								
No	12·5 (117/937)	17·5 (161/918)	11·7 (108/921)	15·2 (139/912)	13·7 (124/904)	10·4 (94/903)	23·7 (215/909)	51·6 (475/920)
Yes	11·5 (7/61)	18·7 (11/59)	21·7 (5/23)	17·4 (4/23)	22·8 (13/57)	6·9 (4/58)	28·8 (17/59)	57·4 (35/61)
Damp:								
None	10·6 (90/853)	15·3 (128/839)	10·7 (90/841)	14·7 (123/834)	13·8 (114/824)	9·7 (80/824)	23·8 (197/829)	50·8 (427/640)
Other rooms†	20·9** (18/86)	25·6* (21/82)	11·1 (9/81)	18·5 (15/81)	17·3 (14/81)	14·3** (12/84)	32·1 (27/84)	60·0 (51/85)
Child's bedroom	24·6** (15/61)	37·3*** (22/59)	31·1*** (19/61)	25·9* (15/58)	17·2 (10/58)	8·9 (5/56)	18·3 (11/60)	56·7 (34/60)
Mould:								
None	10·5 (96/911)	15·6 (140/895)	11·7 (105/896)	15·3 (136/889)	13·3 (117/878)	9·8 (86/882)	23·2 (206/888)	52·1 (468/899)
Other rooms†	23·4* (11/47)	32·6** (15/46)	12·8 (6/47)	17·0 (8/47)	23·4 (11/47)	20·0 (9/45)	35·6 (16/45)	46·7 (21/45)
Child's bedroom	38·1*** (16/42)	43·6*** (17/39)	21·4 (9/42)	26·3 (10/38)	26·3* (10/38)	7·9 (3/38)	30·8 (12/39)	55·0 (22/40)

*$p<0·05$, **$p<0·01$, ***$p<0·001$ compared with prevalence in uppermost category. †Present in one or more rooms other than child's bedroom.

between damp walls and mould: 48% (71/147) of the homes affected by dampness were reported to be mouldy, and 80% (71/89) of the mouldy homes were reported to be damp. Mould seemed to have a greater effect on wheeze than did damp. In a model that included damp walls anywhere in the house the effect of mould remained significant ($\chi^2=7·52$, df=1), whereas the effect of dampness independent of mould was negligible ($\chi^2=0·60$, df=1).

The relations between housing conditions and chest colds, cough at night, cough during the day, and nasal discharge were investigated in similar multiple logistic regression models with each respiratory symptom in turn as the outcome variable. The association between mould and chest colds was independent of housing tenure, number of people per room, number of smokers, and gas cooking (odds ratio 2·08 (1·22-3·51); $\chi^2=7·26$, df=1). Inclusion of wheeze during the past year as a further explanatory variable reduced this effect so that it was no longer significant, although it remained in the same direction (odds ratio 1·43 (0·77 to 2·70)). At least part of the association between chesty colds and mould thus seemed to be a consequence of a recent tendency to wheeze.

The weaker associations of cough at night and during the day with mould in the home were entirely explained by their common association with rented housing. After adjustment for tenure the odds ratios for cough at night and cough during the day associated with mould were 0·92 and 0·95, respectively, and the effect of mould on nasal discharge remained in the expected direction but was non-significant (odds ratio 1·61 (0·89 to 2·90); $\chi^2=2·42$, df=1). Further adjustment for the effects of number of people per room, number of smokers, and gas cooking made little difference to these results.

Objective evidence of airways reactivity was collected to investigate the possible contribution of bias in reporting to the observed association between wheeze and mould in data from this and a previous questionnaire.[17] As expected, wheeze during the past year was more prevalent among the children who had bronchospasm after exercise. If no reporting bias had existed this relation would have been independent of housing conditions. In fact, for any given degree of bronchial lability a parental report of wheezing was more commonly obtained for children from homes with mould (table II). In a logistic regression model with wheeze during the past year as the outcome bronchial lability was included as a continuous explanatory variable. Its relation to wheeze was roughly linear (χ^2 for quadratic term=1·05, df=1) and was modelled as such. The effect of mould in the home was independent of lability (odds ratio 3·50 (1·95-6·47); $\chi^2=16·1$, df=1) and constant across the range of lability observed (χ^2 for interaction term=0·10, df=1). This odds ratio of 3·5 was comparable with the odds ratio of 3·7 obtained in the earlier model, which excluded lability; this implies that the relation between mould and wheeze was largely unrelated to measurements of airways reactivity.

TABLE II—*Prevalence (%) of wheeze in past year related to mould in home and bronchial lability induced by exercise. Numbers of children are given in parentheses*

Lability index*	No mould	*Mould in any room*	Total
<0·8	48·6 (17/35)	60·0 (3/5)	50·0 (20/40)
0·8-0·89	11·1 (7/63)	44·4 (4/9)	15·3 (11/72)
0·9-0·99	8·9 (34/383)	33·3 (10/30)	10·7 (44/413)
≥1·0	6·6 (20/303)	14·7 (5/34)	7·4 (25/337)
Total	10·9 (86/792)†	30·9 (25/81)‡	12·7 (111/873)†‡

*Forced expiratory volume in one second after exercise divided by that before exercise.
†Includes eight children tested while receiving treatment, all of whom wheezed.
‡Includes three children tested while receiving treatment, all of whom wheezed.

The higher prevalence of reported wheeze among children from homes with mould for any degree of airways reactivity suggested that reporting bias explained a substantial part of the association of wheeze with damp or mouldy housing. Bronchospasm after exercise (lability index <0·8) was, however, more common among the children from homes with mould. On the generous (but not unreasonable) assumption that all the children receiving drug treatment for asthma who were tested had reactive airways, the prevalence of abnormality was 9·9% (8/81) among children from homes with mould compared with 5·4% (43/792) among the remainder (table II). This difference was in the expected direction, although it did not reach significance ($\chi^2=1·90$, df=1). A non-parametric comparison of the entire distribution of lability in children from homes with and without mould was made using normal scores from the RANK procedure in SAS[22] to correct for the pronounced skewness. The difference between the two groups was negligible (Student's $t=0·4$, df=860).

Discussion

This study confirms the finding of previous surveys in one part of Edinburgh and suggests that an association between damp or mouldy housing and respiratory symptoms is not confined to specific council estates or to rented as opposed to owner occupied housing.[11,17] The association between mould and wheeze meets many of the criteria for an epidemiological association to be considered causal: it is strong, relatively specific when compared with other symptoms, consistent with previous studies, and free of substantial confounding by other factors studied.[24] Biologically plausible causal mechanisms can be proposed, and, assuming that duration of exposure is greatest when the child's bedroom is affected by mould or damp, there is a suggestion of a dose-response relation.

The association of wheeze with damp or mouldy housing was of particular interest not only because confounding by other features of the home environment was unlikely but also because a primary association with wheeze might account for the effect of damp, mouldy housing on other respiratory symptoms related to asthma. Furthermore, wheeze was the symptom for which a causal link with damp housing conditions was most plausible biologically.

The prevalence ratio for wheeze in the past year when homes with and without mould were compared is remarkable in view of the lack of correlation of most social or environmental variables with childhood asthma.[25,26] The study sample was drawn from the general population and permitted an estimate of the importance to public health of this association. If no child in the population of 1000 had been exposed to mould in the home 105 cases of wheeze during the past year would have been expected, based on 96 cases in 911 children (table I). As 123 cases were seen mould in the home accounted for 14% (18/123) of all cases of wheeze. This fraction of the population attributable risk varied with the prevalence of exposure, being 6% (4·5/75) for children from owner occupied homes but 26% (12·5/49) for children from rented homes. These proportions are certainly much greater than any corresponding hazards from cooking or heating fuels.

In a study of adults 43% of those living in areas of poor quality housing associated respiratory symptoms with their housing whereas in areas of good housing only 10% did so.[12] Differences such as this may reflect a causal relation, but they raise the possibility that reports of health state and particularly of respiratory symptoms may be influenced by perceptions of the

home environment. The present study showed that at any given level of airways reactivity induced by exercise the prevalence of wheeze reported by parents of children from homes with mould was substantially higher than the prevalence reported for children from unaffected homes. Interpretation of these results depends on the validity of the exercise challenge as an objective indicator of respiratory disease.

Exercise was chosen because it is a common physiological challenge and therefore positive findings can be considered to have intrinsic validity. Pharmacological challenge tests may be more sensitive to minor degrees of airways reactivity, but they can induce bronchospasm in many non-wheezy children, which makes the interpretation of positive results less certain.[27] Although wheeze and bronchial lability were clearly related, in two thirds of the wheezy children the forced expiratory volume in one second after exercise was within 10% of the value determined before exercise. Any assessment of change in a spirometric index is sensitive to errors of measurement, particularly in this young age group. Repeating the measurements in the same population of children suggested that forced expiratory volume in one second was the most reproducible spirometric index, but its coefficient of variation within subjects on any given occasion was 8·5%; hence the lability index was subject to substantial random errors of measurement and individual subjects were misclassified.

Though lack of sensitivity and random errors in the test procedure may have reduced the power of the study to detect a true relation between reported mould and bronchial lability, the negative findings do not exclude an association. These limitations cannot, however, explain the different relations between wheeze and lability in the children from homes with and without mould. This difference could be explained if exposure to mould commonly resulted in a syndrome (or a subtype of asthma) that caused wheeze but was not associated with airways reactivity to exercise. By its very nature this is a difficult proposition to test objectively, but it is unlikely for two reasons. Firstly, epidemiological and clinical evidence supports the concept of childhood asthma as a single disease, the cardinal symptom of which is wheeze.[27 28] Secondly, the most plausible causal mechanism for any association between mould and wheeze is allergy to airborne spores, but atopic skin reactions to common antigens are associated with more frequent wheeze,[29] and children who wheeze more frequently are more likely to show airways reactivity.[27]

An alternative argument might be that bronchospasm induced by exercise reflects an underlying susceptibility to asthmatic attacks rather than the activity of the disease itself. In this case the prevalence of symptoms might depend on both host factors (non-specific bronchial hyperreactivity) and the "dose" of trigger factors in the environment (including mould spores). The results presented in table II could be interpreted as showing this, given that lability induced by exercise was an imprecise measure of underlying airways reactivity and that mould may not be a trigger for all susceptible children. Such a distinction between host and environmental factors is, however, called into question by observations that when patients with sensitivity to house dust mite move to an environment free of allergens the response of their bronchi to inhaled histamine is reduced.[30] This suggests that non-specific bronchial hyperreactivity can result from long term exposure to allergen and is a manifestation of asthma rather than a cofactor in its aetiology.

The most straightforward explanation of the discrepancy between the questionnaire and clinical data is that awareness of dampness or mould in the home as a determinant of parental reporting of symptoms; this would account for much of the observed association between mould and respiratory symptoms. The use of the term reporting bias should not be misunderstood. It does not mean that the accuracy of reporting by occupants of homes with mould is necessarily poorer; recall of symptoms for children in homes not affected by mould may be less complete. This reporting bias, however, implies that further studies of this relation are unlikely to be valid if they rely solely on information from questionnaires. An alternative source of reporting bias which has not been considered here, is the effect of the child's symptoms on parental awareness of adverse conditions in the home. Ambient humidity and airborne fungal spores are being measured in subsamples of the study population to address this issue.

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Oldigs, M., Jorres, R., Magnussen, H. "Acute Effect of Passive Smoking on Lung Function and Airway Responsiveness in Asthmatic Children" Joint Meeting SEP-SEPCR Barbican Centre, London, September, 1990.

SUMMARY: In 11 children with bronchial asthma (age range 8-13 yr, 10 boys, 1 girl) we studied the effect of an one hour exposure at rest during passive cigarette smoking (20 ppm CO) or Sham. Nine of the subjects were on regular therapy with inhaled B2-agonists and DSCG. Both components were withheld at least six hours prior to each study session. Exposure was performed in an environmental chamber. Before and immediately after exposure, lung function and symptom scores were determined. After exposure, a histamine inhalation challenge was performed to determine the concentrations which caused a 100% increase in SRaw, PC100SRaw, and a 20% fall in FEV1, PC20FEV1. Mean (SD) SRaw before and after Sham was 8.7 (3.6) and 9.0 (3.2) cmH20*s, mean FEV1(SD) was 1.97 (0.32) and 1.98 (0.40) l, respectively. Before and after cigarette smoking, mean SRaw (SD) was 10.4 (5.3) and 9.4 (3.3) cmH20*s, mean FEV1 (SD) was 1.95 (0.37) and 1.94 (0.35) l, respectively. Geometric mean (SD) PC100SRaw and PC20FEV1 after Sham was 1.39 (3.0) and 0.70 (2.7) mg/ml, after passive smoking 1.65 (2.5) and 0.96 (2.3) mg/ml respectively. There was no statistical difference in lung function and PC-values between Sham and passive cigarette smoking. The main symptoms during passive smoking were eye and nasopharyngeal irritation. Our observations suggest that in children with mild bronchial asthma one hour of passive cigarette smoking does not cause airway obstruction or changes in bronchial responsiveness.

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ACUTE EFFECT OF PASSIVE SMOKING ON LUNG FUNCTION AND AIRWAY RESPONSIVENESS IN ASTHMATIC CHILDREN [a]

Maike Oldigs MD, Rudolf Jörres MS, Helgo Magnussen MD

Krankenhaus Grosshansdorf
Zentrum für Pneumologie und Thoraxchirurgie
LVA Freie und Hansestadt Hamburg

Running title: Passive smoking in childhood asthma

Correspondence: Helgo MAGNUSSEN
Krankenhaus Grosshansdorf
Wöhrendamm 80
2070 Grosshansdorf
FRG
Telephone: FRG 4102 - 601 150

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SUMMARY

In 11 children with bronchial asthma (age range 8-13 yr, 10 boys, 1 girl) we studied the effect of an one hour exposure at rest during passive cigarette smoking (20 ppm CO) or Sham. Nine of the subjects were on regular therapy with ihhaled β_2-agonists and DSCG. Both components were withheld at least six hours prior to each study session. Exposure was performed in an environmental chamber. Before and immediately after exposure, lung function and symptom scores were determined. After exposure, a histamine inhalation challenge was performed to determine the concentrations which caused a 100% increase in SRaw, $PC_{100}SRaw$, and a 20% fall in FEV_1, $PC_{20}FEV_1$. Mean (SD) SRaw before and after Sham was 8.7 (3.6) and 9.0 (3.2) $cmH_2O \cdot s$, mean FEV_1 (SD) was 1.97 (0.32) and 1.98 (0.40) l, respectively. Before and after cigarette smoking, mean SRaw (SD) was 10.4 (5.3) and 9.4 (3.3) $cmH_2O \cdot s$, mean FEV_1 (SD) was 1.95 (0.37) and 1.94 (0.35) l, respectively. Geometric mean (SD) $PC_{100}SRaw$ and $PC_{20}FEV_1$ after Sham was 1.39 (3.0) and 0.70 (2.7) mg/ml, after passive smoking 1.65 (2.5) and 0.96 (2.3) mg/ml, respectively. There was no statistical difference in lung function and PC-values between Sham and passive cigarette smoking. The main symptoms during passive smoking were eye and nasopharyngeal irritation.

Our observations suggest that in children with mild bronchial asthma one hour of passive cigarette smoking does not cause airway obstruction or changes in bronchial responsiveness.

KEY WORDS:

Passive Smoking, Lung Function, Bronchial Hyperresponsiveness, Childhood Asthma

INTRODUCTION

Subjects with bronchial asthma are characterized by airway hyper-responsiveness to a variety of stimuli. Cigarette smoke is considered to be a common stimulus which may affect subjects with asthma (1-3).

In children, the adverse effect of chronic passive smoking on respiratory symptoms has received increasing attention (4-7). In some of these investigations an association between parental smoking habits and acute lower respiratory illness (8-12), respiratory symptoms (13-16), prevalence and severity of asthma (13,17,18), impaired lung function and bronchial responsiveness (10,12,13,16,17,19-23) could be demonstrated.

In contrast to chronic exposure, little is known on the acute effect of passive smoking in children. We therefore studied symptoms, lung function and airway responsiveness of children with bronchial asthma before and after one hour exposure to cigarette smoke as compared to control conditions.

MATERIAL AND METHODS

Patients

We investigated 11 children with allergic bronchial asthma (10 boys, 1 girl) ranging in age from 8 to 13 years (mean (SD) 10.4 (1.4) yr). Individual patient characteristics are given in table 1.

In all children the diagnosis of bronchial asthma was made up within at least 1 year before entering the study and patients had been followed up for a longer period of time on an out-patient basis. The children were not selected on the basis of symptoms induced by cigarette smoke.

Diagnosis was based on typical symptoms, reversible airflow obstruction, bronchial hyperresponsiveness to histamine and a positive prick skin test to at least one common allergen (Allergopharma, Reinbek, FRG). Six out of 11 patients showed an increase in total IgE (>150 IE/ml), and 6 children an increase of eosinophils in peripheral blood ($>300/mm^3$).

In all subjects the severity of asthma required a long-term therapy, which had to be continued in 9 of 11 children during the study period. All children on therapy received disodium cromoglycate, two puffs two to four times per day. Each puff of disodium cromoglycate (1 mg) was combined with 0.05 mg fenoterol (Ditec^R) or 0.5 mg reproterol (Aarane^R) as a β_2-agonist. One subject took two additional puffs of 200 µg beclomethasone dipropionate. In all children, this therapeutic regime was sufficient to control the disease and allow normal activities. This is also reflected by the magnitude of morning (before therapy, PEF_{min}) and maximum daytime peak flow values (PEF_{max}), which were measured regulary (table 1).

In the 9 asthmatic children receiving regular therapy, the activity of the disease allowed to discontinue inhalation therapy at least six hours prior to each study session without precipitating symptoms or deteriorating lung function (subject 6 continued beclomethasone inhalation during the study period).

Spirometry, measured at least six hours after inhaling a bronchodilator was within normal limits. In all children the provocative concentration of inhaled histamine necessary to decrease FEV_1 by 20% as compared to baseline was less than 8 mg/ml (table 1), thus demonstrating airway hyperresponsiveness (see Histamine inhalation challenge).

During the study period and within the two weeks preceeding the study no child suffered from an upper respiratory tract infection, experienced an uncommon burden of allergen or reported on any other trigger which may worsen asthma; therefore all included children were considered to be currently clincally stable.

None of the children had ever actively smoked cigarettes, six of them were exposed to cigarette smoke at home (table 2).

Children and parents were informed about the aim of the study and gave their consent.

Cigarette smoke exposure

Exposure chamber

The study was performed in a 24 m^3 exposure chamber. To ensure homogenous concentration of cigarette smoke the air was moved by fans in

a spiral form. Sampling ports were distributed within the chamber to check for gradients of gas concentrations and particle density. Cigarette smoke was generated by a smoking machine designed in our laboratory which took 1 puff per cigarette per minute (according to DIN 10240). To achieve the target concentration of about 20 ppm CO, on average 2 cigarettes were smoked simultaneously. We used filter cigarettes of a leading brand with a nicotine content of 0.9 mg and tar content of 13 mg per cigarette.

Measurement of exposure conditions

The level of cigarette smoke exposure was determined by measuring CO, NO_x, particle density, nicotine, acetaldehyde, formaldehyde, acrolein and ammonia. Concentration of CO was measured continuously by an infrared gas analyzer (Unor 6N, Maihak AG, Hamburg, FRG) whose calibration was checked daily by a certified span gas (Linde AG, Unterschleißheim, FRG). Concentration of NO_x was measured by a chemiluminescence nitrogen oxides analyzer (8840, Monitor Labs Inc., San Diego, CA, USA) which was calibrated regularly by a permeation tube calibrator (Model 8550, Monitor Labs Inc., San Diego, CA). Particle density was monitored continuously by measuring optical particle density (RAM-1, GCA/Environmental Instruments, Bedford, Mass., USA) using a 4 µm precollector. Calibration of optical particle density was done in regular intervals gravimetrically by taking filter probes (Millipore, FALP 03700, Typ FA) from total sampling volumes of 17-73 litres of air. Nicotine, acetaldehyde, formaldehyde, acrolein and ammonia were determined using commercially available sample tubes and filters at sampling volumes ranging between 3 and 100 litres of air. Analysis was done by gas chromatography (nicotine), by high performance

liquid chromatography (acetaldehyde, formaldehyde, acrolein) and by the indophenol method VDI 2461 (ammonia). Temperature and relative humidity were measured at the beginning and at the end of each exposure.

Estimation of chronic smoke exposure

To estimate chronic passive smoke exposure at home, urinary cotinine concentrations were determined in triplicate from morning urine specimens collected at the second study day. Determination was made in an environment free of smoking. Urine was stored at -20 °C until assayed. Cotinine was measured by a radioimmunoassay procedure (24).

Assessment of symptoms

Before and immediately after exposure the chest of each subject was auscultated by one of us (M.O.). To estimate severity of symptoms induced by exposure, the children and their parents were instructed to check an ordinal scale ranging from 0 to 10 in order to determine severity of eye, nose irritation, throat irritation, cough, chest tightness and headache. Zero indicated no perceptible symptom, 10 almost intolerable severity of the respective symptom.

Lung Function Measurement

Airway resistance (Raw) during breathing at 1 Hz and thoracic gas volume (TGV) were measured by a volume-constant body plethysmograph (Bodytest, E. Jaeger, Würzburg, FRG) connected to a Computer (PDP 11/04, Digital Equipment Corp., Maynard, MA, USA). Airway resistance was multiplied by the corresponding thoracic gas volume to obtain specific airway resistance (SRaw). Airway resistance was measured during up to 4 breathing cycles. FEV_1 was assessed by a pneumotachygraph immediately after body plethysmography. Measurements were repeated 4 times. For analysis, the average of 4 values of SRaw and the average of the two maximum values of FEV_1 was taken.

Histamine Inhalation Challenge

Bronchial challenge with histamine was done according to the guidelines of Chai et al. (25) using a breath-synchronized pressure valve. The aerosols were generated during 0.6 sec. at the beginning of 5 slow inspirations from FRC to TLC, the nebulizer output being 80 µl of solution per 5 nebulizations. Saline solutions of histamine diphosphate (Sigma Chemie, Deisenhofen, FRG) were prepared daily. After inhaling buffer solution, the subjects inhaled doubling concentrations of histamine, starting with 0.05 mg/ml histamine. Lung function was measured 1 and 3 min after inhalation. The inhalation was stopped after at least a 100 % increase of SRaw and a 20 % fall in FEV_1. Dose-response curves were constructed by plotting SRaw and FEV_1 against log histamine concentration. By linear interpolation, the provocative

concentrations of histamine (in mg/ml) were computed necessary to increase SRaw by 100 % ($PC_{100}SRaw$) and to decrease FEV_1 by 20 % ($PC_{20}FEV_1$) as compared to baseline. With this method, hyperresponsiveness was assumed if PC-values were below 8 mg/ml (26).

Experimental Protocol

Each subject was studied at three days within a two week period. All investigations were performed at least six hours after the last application of therapy.

On the first day recent history was taken and a physical investigation performed. Lung function and airway responsiveness to inhaled histamine were measured. In case of stable clinical conditions, normal lung function and airway hyperresponsiveness, the children and their parents were instructed in the experimental procedure. They were provided with sampling probes for collecting morning urinary specimens.

On the second study day, exposure to ambient air (Sham) and at the third study day exposure to cigarette smoke was performed.

On exposure days, subjects rested for 10 minutes after entering the laboratory. After auscultation of the chest, assessment of symptoms and measurement of baseline lung function, the children entered the exposure chamber. They were always seated at the same place inside the chamber. Five minutes before the end of exposure, symptoms were assessed again. Immediately after exposure, auscultation of the chest and lung function measurement were performed. Histamine inhalation challenge was started 15 minutes after the end of exposure.

Statistical Analysis

Lung function parameters before and after both exposures and control values were compared to each other by the paired t-test after appropriate Bonferroni correction for multiplicity of tests (27). Log PC-values after both exposures and control values were also compared by the paired t-test. The assumption of normal distribution of data was checked by normal probability plots and tests. Statistical significance was assumed for $p<0.05$.

RESULTS

Exposure conditions

During Sham and cigarette smoke exposure, mean (SD) temperature was 24.1 (1.6) °C and mean relative humidity was 51 (3) %, with no difference between the study days. During passive smoke exposure, mean (SD) total particle density was 2743 (348) $\mu g/m^3$ and nicotine content was 397 (78) $\mu g/m^3$. Mean (SD) concentrations of CO were 20.5 (0.5) ppm, NO_x 0.90 (0.09) ppm, formaldehyde 0.13 (0.01) ppm, acetaldehyde 0.50 (0.05) ppm, acrolein 0.081 (0.017) ppm and ammonia 5.69 (3.35) ppm. During exposure with ambient air, mean (SD) CO was 0.1 (0.3) ppm, and mean (SD) total particle density was 17 (57) $\mu g/m^3$.

Symptoms during exposure

In all of our children, auscultation of the chest was normal before and after exposure to Sham and cigarette smoke, respectively. Eye irritation was experienced by all subjects during smoke exposure (Fig. 1). Nasal congestion was reported by 9/11 children after cigarette exposure and 5/11 after Sham. After smoke exposure, throat irritation occured in 3/11, cough in 0/11, chest tightness in 3/11, and headache in 3/11 children. Except for eye irritation, the frequency and intensity of the symptoms did not differ between cigarette smoke and Sham exposure (Fig. 1).

Variability of baseline lung function

Mean (SD) SRaw before Sham and smoke exposure was 8.7 (3.6) and 10.4 (5.3) $cmH_2O \cdot s$, respectively. These values were not significantly different from each other nor from the mean (SD) SRaw value of 8.5 (2.8) $cmH_2O \cdot s$ measured on study entry (control, table 3).

Mean (SD) FEV_1 before Sham and cigarette smoke was 1.97 (0.32) and 1.95 (0.39) l, respectively. These values were not significantly different from each other nor from the mean (SD) FEV_1 value of 1.95 (0.39) l when entering the study (control, table 3).

Mean (SD) values of individual variation coefficients of the three repeated determinations of SRaw and FEV_1 were 21 (11) and 6 (4) %, respectively.

Lung function changes during exposure

Mean (SD) SRaw before and after one hour exposure to ambient air (Sham) was 8.7 (3.6) and 9.0 (3.2) $cmH_2O \cdot s$, respectively, with no statistically significant difference (table 3). Mean (SD) FEV_1 before and after Sham was 1.97 (0.32) and 1.98 (0.40) l, respectively, with no significant difference. Percentage changes of SRaw and FEV_1 during Sham ranged from -28 to +59% and from -10 to +9%, respectively.

Mean (SD) SRaw before and after one hour exposure to cigarette smoke was 10.4 (5.3) and 9.4 (3.3) $cmH_2O \cdot s$, respectively. Mean (SD) FEV_1 before and after smoke exposure was 1.95 (0.39) and 1.94 (0.35) l, respectively (table 3, Fig. 2). Values before and after exposure were not significantly different from each other. Percentage changes of SRaw and FEV_1 during passive smoking ranged from -37 to +12% and from -25 to +13%, respectively.

Airway responsiveness during exposure

Geometric mean (SD) $PC_{100}SRaw$ and $PC_{20}FEV_1$ at control were 0.85 (2.4) and 0.54 (2.7) mg/ml, respectively (table 4, Fig. 3).

Geometric mean (SD) $PC_{100}SRaw$ and $PC_{20}FEV_1$ measured after Sham were 1.39 (3.0) and 0.70 (2.7) mg/ml, respectively. Geometric mean (SD) $PC_{100}SRaw$ and $PC_{20}FEV_1$ after exposure to cigarette smoke were 1.65 (2.5) and 0.96 (2.3) mg/ml, respectively (table 4, Fig. 3).

$PC_{100}SRaw$ and $PC_{20}FEV_1$ were not significantly different between Sham, cigarette smoke exposure or control.

As determined from Sham and control, the mean (SD) value of individual variability of $PC_{100}SRaw$ and $PC_{20}FEV_1$ was 1.0 (0.5) and 0.9 (0.6) doubling concentrations of histamine, respectively.

DISCUSSION

Our observations demonstrate that in children with mild bronchial asthma one hour passive smoking produced mainly eye irritation but no airway obstruction and no significant changes in bronchial responsiveness to inhaled histamine.

To the best of our knowledge, acute pulmonary response to passive smoke exposure has not been studied in asthmatic children. Previous studies on the acute effect of passive smoking were performed in adult asthmatics. These studies showed conflicting results.

Shephard and coworkers (28) investigated 14 asthmatic subjects during a 2-h cigarette smoke exposure (24 ppm CO) and observed no significant changes in pulmonary function. Dahms et al. (29) reported on 10 asthmatics passively exposed to cigarette smoke (15 - 20 ppm CO) for one hour. These authors found a 21.4% decrease in FEV_1 following smoke exposure in asthmatics compared to normal controls. Knight and Breslin (30) studied 6 patients with asthma who developed a 11% decline in FEV_1 and an increase in bronchial reactivity to inhaled histamine 4 hours after a 1-h smoke exposure (15 - 25 ppm CO). Wiedemann and coworkers (31) examined the acute effect of a 1-h chamber exposure to cigarette smoke (40 - 50 ppm CO) on lung function and airway responsiveness in 9 adult asthmatics. In these subjects no change in lung function was observed, but a small decrease in nonspecific airway

reactivity. Recently, Stankus et al. (32) investigated the effect of an 2 hour exposure to tobacco smoke (8.7 - 14.1 ppm CO) in 21 subjects with asthma who claimed on respiratory symptoms on previous exposure to cigarette smoke. In 7 of these 21 subjects suspected as smoke sensitive asthmatics, they found a significant (> 20%) fall in FEV_1. These findings in adult asthmatics demonstrate that there might be a subgroup of smoke sensitive asthmatics who develop acute airway obstruction without consistent changes in airway responsiveness following passive smoke exposure.

In our group of asthmatic children, after exposure to Sham changes of FEV_1 between -10 and +9% were observed as compared to pre-exposure values. After exposure to passive cigarette smoke, in 9 subjects changes of FEV_1 were within this range. Subject #3 showed an increase in FEV_1 by 13% after smoke exposure in contrast to an decrease of 10% after Sham. Subject #7 showed a decrease in FEV_1 by 25% after smoke exposure as compared to an increase of 5% after Sham. In both subjects, changes in FEV_1 were larger than corresponding changes in SRaw. Analysis of the spirometric curves, however, did not reveal any sign of deficient cooperation in both subjects. According to our study protocol, baseline lung function measurement was performed three times on three different study days. Mean coefficients of variation were 6% for FEV_1 and 21% for SRaw which is well within the reproducibility reported in adult subjects (33). Therefore, we do not believe that our inability to demonstrate an adverse acute effect of passive cigarette smoking on lung function was due to an insufficient reproducibility of lung function data.

Airway hyperresponsiveness to inhaled histamine in terms of $PC_{20}FEV_1$ and $PC_{100}SRaw$ was assessed three times on three different study days. The two challenges without previous smoke exposure (control, Sham) showed a variability of plus minus one doubling concentration of histamine, which is

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within accepted limits (33,34). Therefore, it is unlikely that our findings were due to a weak reproducibility of bronchial responsiveness measurement. However, it seems to us that in children further investigations on the possible interaction between DSCG and passive smoking should be done.

Nine out of 11 asthmatic children were under regular therapy consisting of inhaled β_2-agonists and disodium cromoglycate (and in subject #6 of additive 400 µg beclomethasone diproprionate). The duration of the effect of inhaled β_2-agonists on airway tone and bronchial responsiveness is within 3 - 5 hours (35). Therefore, as we started exposure at least 6 hours after the last inhalation therapy, an influence of β_2-agonists on our data seems to be unlikely.

This may however not be true for disodium cromoglycate (DSCG). There are conflicting data on the protective effect of DSCG on airway responsiveness. Most authors agree that a significant protection against airway obstruction induced by histamine or methacholine could not be substantiated (36). Recently it has been shown that long term treatment with DSCG may modify the level of bronchial hyperresponsiveness (37).

In our study all children showed bronchial hyperresponsiveness to inhaled histamine, irrespective of the foregoing therapy with DSCG. Three of the 9 children with DSCG showed an increase in airway responsiveness after passive cigarette smoking, the remaining children an decrease in airway responsiveness. In comparison, one child without therapy showed an increase and the other one without therapy showed a decrease in hyperresponsiveness after smoke exposure. Our inability to demonstrate an effect of passive smoke exposure on airway responsiveness in the presence of hyperresponsiveness to inhaled histamine is unlikely to be explained by the pharmacologic profile of DSCG.

In the present study the level of cigarette smoke exposure was characterized by several components which may be potential irritants per se. It has been suggested that substances like CO (38), NO_2 (39), formaldehyde (40) and aerosolized nicotine (41) may produce upper respiratory symptoms. The threshold concentration of NO_2 which causes an increase in hyper-responsiveness during resting ventilation is about 0.25 ppm (39). In our experiments, total NO_x concentration was about 1 ppm, however, the reactive component NO_2 was measured to be less than 3% of the total concentration of NO_x. Acrolein (an unsaturated aldehyde) has been demonstrated to decrease pulmonary function in guinea pigs at concentrations of at least 0.31 ppm and to produce transient bronchial hyperresponsiveness (42,43). In our study the concentration of acrolein was in the range of 0.1 ppm. For saturated aldehydes like formaldehyde it has been reported that in asthmatics exposure to concentrations up to 3 ppm for 1 - 1.5 hour did not cause statistically significant decrements in pulmonary function (40,44). Under our exposure conditions, formaldehyde concentration was about 0.13 ppm. Therefore, our concentrations of the cigarette smoke components were always lower than those effective in the single component exposure studies. Because we did not see an effect of passive smoking on lung function or airway responsiveness, synergistic effects between the constituents of cigarette smoke seems to be unlikely.

By measuring urinary cotinine concentration which is an accepted biological marker of chronic exposure to passive smoke (45-48), we were able to identify 6 out of 11 asthmatic children with reported passive smoke exposure at home (table 2). This observation confirms that many children are exposed by the smoking habits of their parents. Since the purpose of our study was to investigate the acute effects of passive smoking and since we did not find an

effect and could not identify an active component of cigarette smoke in our experiments, it is difficult to compare our data with those of chronic exposure studies. Chronic exposure has been demonstrated to increase bronchial responsiveness and to impair lung function (10,12,13,16,17,19-23). Our data regarding short-term exposure are by no means contradictory to these observations. In addition, chronic passive smoke exposure may induce changes in the airways which mask airway response to acute exposure. From our data this hypothesis can not be proved, however, it would be of interest to study the acute airway response of asthmatic children with and without chronic smoke exposure.

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LEGENDS TO FIGURES

Figure 1 Median and 90%-percentil of symptom score after Sham and passive smoke exposure.

Figure 2 FEV_1 (l) and SRaw ($cmH_2O \cdot s$) before and after exposure (Sham, Passive Smoking) and at the control day.

Figure 3 Airway responsiveness to inhaled histamine after exposure (Sham, Passive Smoking) and at the control day.

Legend to Table 1:

[a]VC: inspired vital capacity.

[b]Geometric mean values and geometric standard deviations of mean.

[c]Therapy: B = inhaled beta-2-agonists, D = disodium cromoglycate, CI = inhaled corticosteroids.

For definitions see text.

Legend to Table 4:

[a]Geometric mean values and geometric standard deviations of mean.

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TABLE 1 - Individual data of patients

Patient No.	Sex	Age yr	Weight kg	Height cm	Atopy	IgE IE/ml	Eosinophils counts/mm^3	PEF_{min} l/min	PEF_{max} l/min	VC^a l_{BTPS}	FEV_1 %pred	$PC_{20}FEV_1^b$ mg/ml	$Therapy^c$
1	m	12	50	165	+	92	563	400	480	3.68	97	0.09	B,D
2	m	13	42	154	+	114	350	280	330	2.18	76	0.34	B,D
3	m	11	35	142	+	524	422	320	440	2.35	97	0.73	B,D
4	m	9	38	140	+	219	100	300	380	2.46	110	1.25	B,D
5	m	10	35	150	+	518	441	280	340	2.48	88	1.72	B,D
6	m	11	40	149	+	146	319	300	380	2.60	111	1.02	B,D,iC
7	m	11	41	151	+	101	181	330	400	2.60	107	1.13	B,D
8	m	9	40	141	+	269	143	240	270	1.90	85	0.12	B,D
9	m	8	26	137	+	137	147	210	330	1.82	90	1.28	-
10	m	10	36	142	+	361	422	280	350	3.00	130	0.46	B,D
11	w	10	35	143	+	185	293	150	220	2.20	98	0.30	-
Mean		10.4	38	147		242	307	281	356	2.48	99	0.77	
SD		1.4	6	8		159	149	65	73	0.52	15	0.55	

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TABLE 2 - Urinary cotinine concentration and reported parental smoking habits

Patient No.	cotinine (ng/ml)	paternal smoking	maternal smoking
1	11	+	-
2	8	+	-
3	34	-	-
4	4	+	-
5	2	-	-
6	1	-	+
7	3	-	+
8	0	-	-
9	11	+	-
10	0	-	-
11	0	-	-

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TABLE 3 - SRaw (in $cmH_2O \cdot s$) and FEV_1 (in l) before (pre) and after (post) exposure to ambient air (Sham) or passive smoke and at the control day

Patient No.	CONTROL		SHAM				PASSIVE SMOKE			
	SRaw	FEV_1	SRaw		FEV_1		SRaw		FEV_1	
			pre	post	pre	post	pre	post	pre	post
1	13.2	2.68	12.5	10.6	2.60	2.84	9.9	11.1	2.76	2.81
2	8.1	1.74	5.9	7.9	1.93	1.86	8.6	9.4	1.84	1.82
3	10.7	1.75	12.6	12.8	1.75	1.57	9.6	8.8	1.74	1.97
4	10.1	1.90	4.6	7.3	2.13	2.11	11.1	9.3	1.83	1.84
5	10.5	1.86	11.9	12.7	1.71	1.75	14.3	14.0	1.47	1.55
6	8.1	2.30	9.0	7.8	2.27	2.32	10.5	8.8	2.23	2.26
7	5.2	2.28	5.8	4.2	2.21	2.33	4.6	4.4	2.33	1.74
8	4.0	1.52	6.6	7.2	1.76	1.75	6.4	6.2	1.79	1.78
9	5.4	1.47	3.5	4.4	1.82	1.69	5.5	5.4	1.59	1.72
10	10.8	2.33	13.9	13.0	2.07	2.10	23.9	15.0	2.21	2.13
11	7.8	1.64	9.7	10.6	1.47	1.50	9.7	10.6	1.63	1.71
Mean	8.5	1.95	8.7	9.0	1.97	1.98	10.4	9.4	1.95	1.94
SD	2.8	0.39	3.6	3.2	0.32	0.40	5.3	3.3	0.39	0.35

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TABLE 4 - Histamine concentration (mg/ml) necassary to increase SRaw by 100% ($PC_{100}SRaw$) or to decrease FEV_1 by 20% ($PC_{20}FEV_1$) after 1 hour exposure to ambient air (Sham) or to passive smoke and at the control day

	CONTROL		SHAM		PASSIVE SMOKE	
Patient No.	$PC_{100}SRaw$	$PC_{20}FEV_1$	$PC_{100}SRaw$	$PC_{20}FEV_1$	$PC_{100}SRaw$	$PC_{20}FEV_1$
1	0.25	0.09	0.51	0.27	0.30	0.21
2	0.92	0.34	5.81	0.78	6.40	1.10
3	1.60	0.73	0.38	0.11	1.24	1.05
4	1.12	1.25	2.38	0.79	1.17	0.87
5	1.45	1.72	4.59	1.68	3.16	2.64
6	2.12	1.02	3.83	1.71	6.90	3.03
7	1.07	1.13	0.59	0.60	1.45	1.57
8	0.12	0.12	0.62	0.67	1.01	1.14
9	1.85	1.28	4.80	4.22	1.40	0.75
10	0.81	0.46	0.37	0.33	0.70	0.27
11	0.66	0.30	1.24	0.68	2.79	1.00
Mean[a]	0.85	0.54	1.39	0.70	1.65	0.96
SD	2.40	2.70	3.00	2.70	2.50	2.30

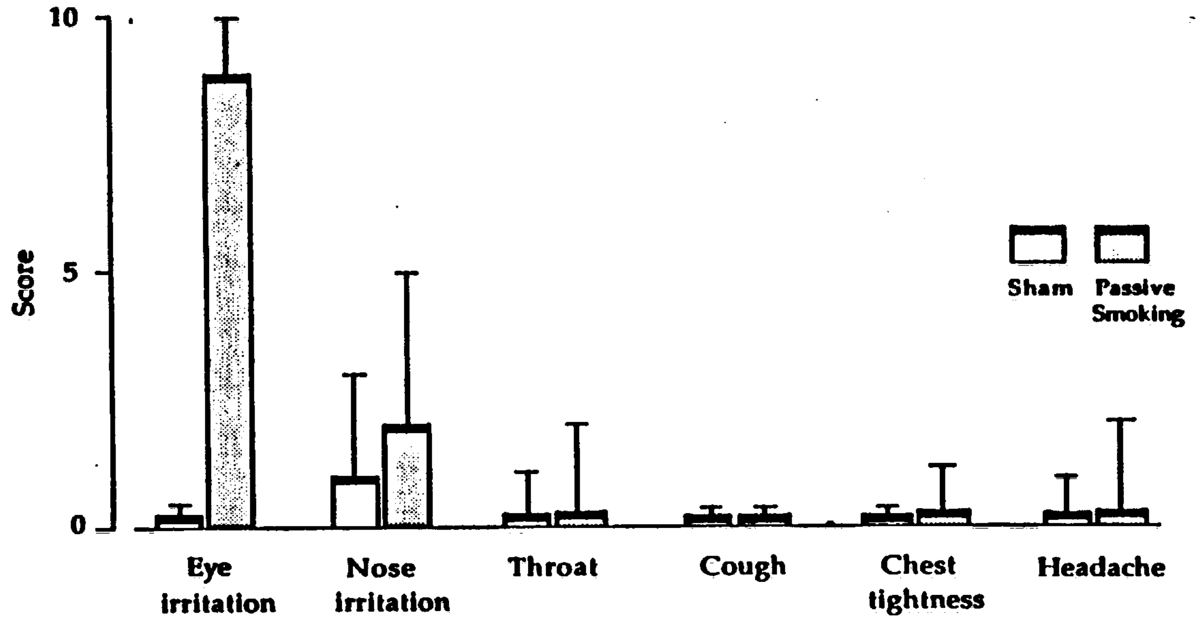

Fig. 1. Median and 90%-percentil of symptom score after Sham and passive smoke exposure.

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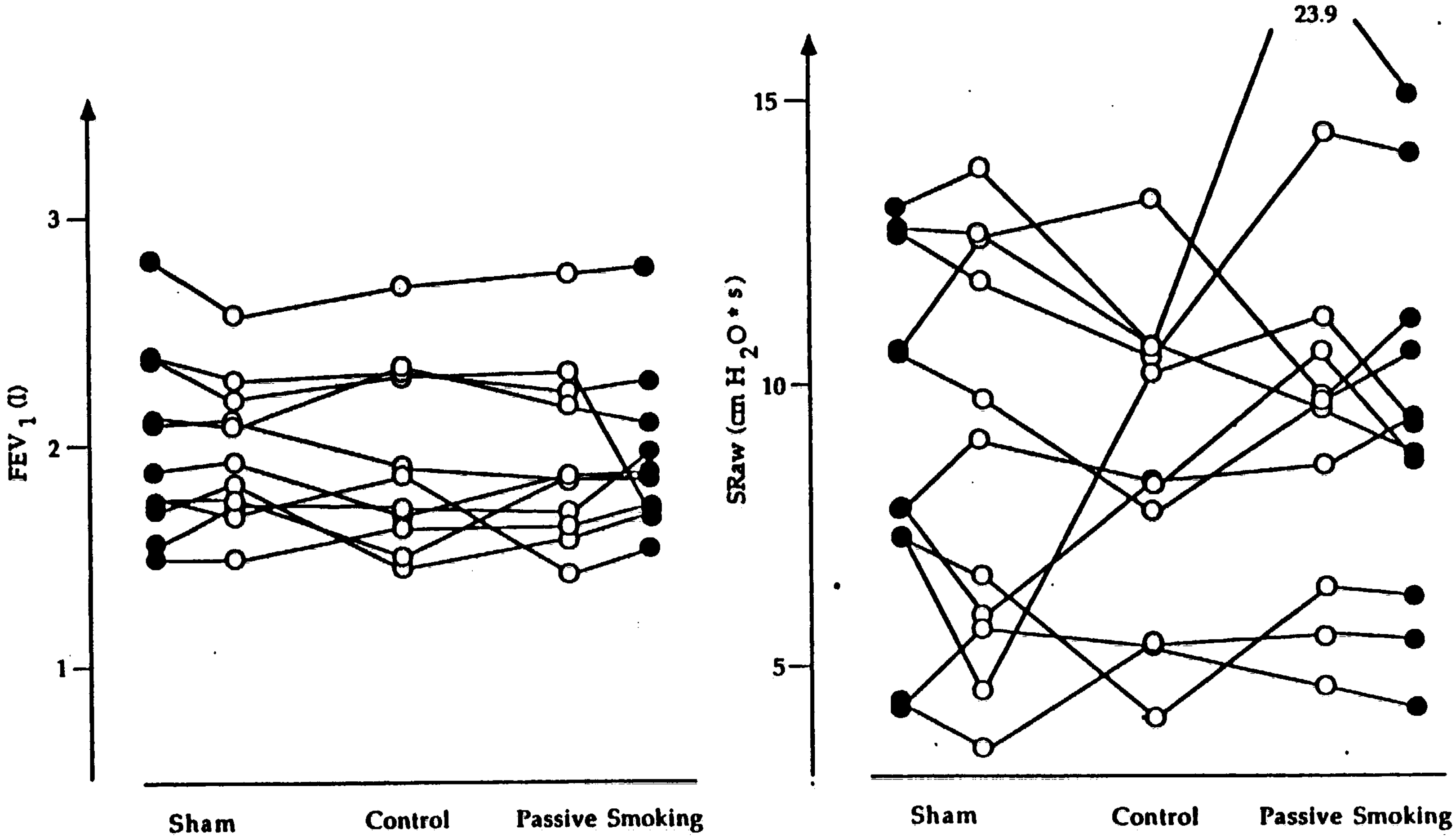

Fig. 2. FEV_1 (l) and SRaw (cmH_2O*s) before (○) and after (●) exposure (Sham, Passive Smoking) and at the control day (○).

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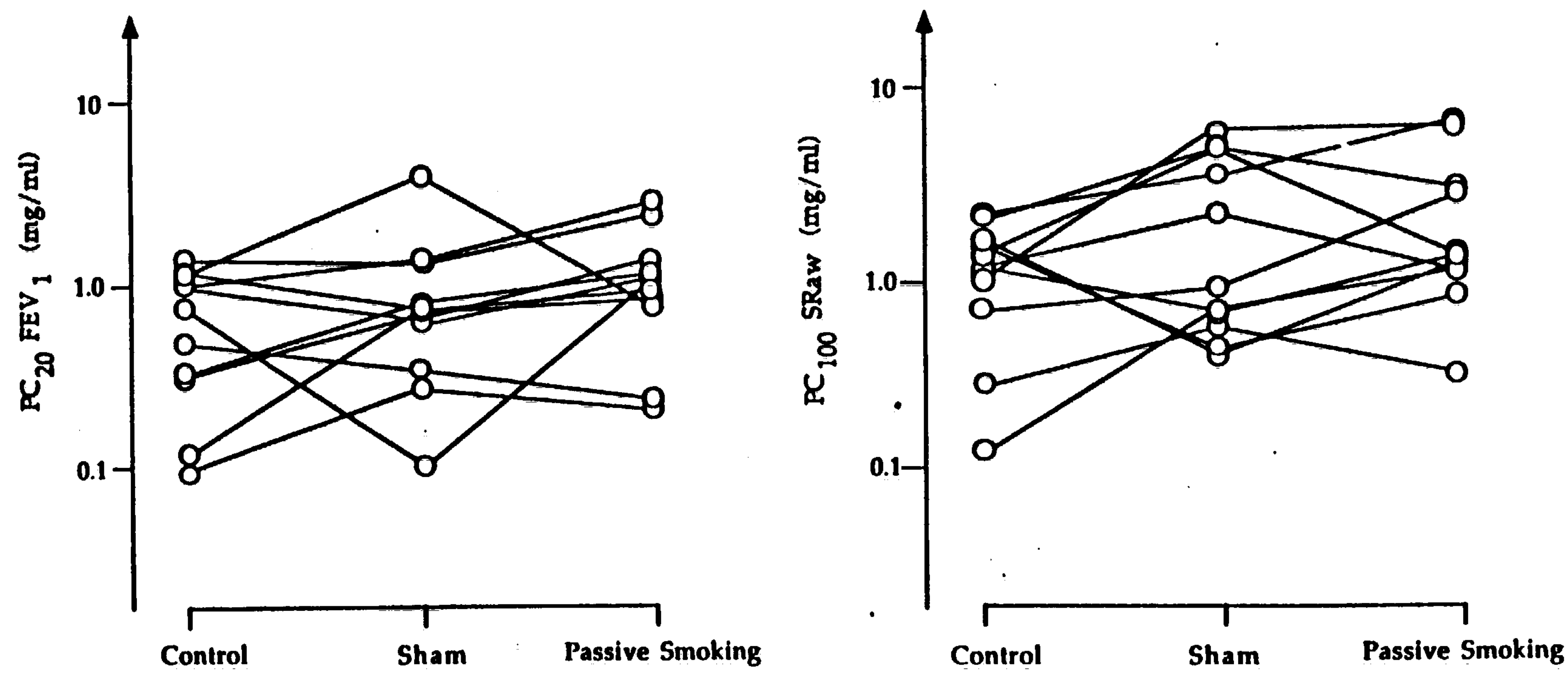

Fig. 3. Airway responsiveness to inhaled histamine after exposure (Sham, Passive Smoking) and at the control day.

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Sherman, C.B., Tosteson, T.D., Tager, I.B., Speizer, F.E., Weiss, S.T. "Early childhood predictors of asthma" Am J Epidemiol 132(1): 83-95, 1990.

ABSTRACT. To investigate potential risk factors for the development of childhood asthma, the authors undertook a longitudinal study using a cohort of 770 children aged 5-9 years from East Boston, Massachusetts, that has been under study since 1975. The disease outcome considered was age at first onset of asthma, as determined by parental or self-reporting of a physician's diagnosis. Potential risk factors were evaluated specifically in relation to their presence antecedent to a diagnosis of asthma. Standardized questionnaires were used to obtain childhood illness histories, environmental exposures, and the asthmatic and atopic statuses of first-degree relatives. Ninety-one cases of asthma were identified from 1975 to 1988 (57 males and 34 females). Significant sex-adjusted relative risk estimates were seen for antecedent pneumonia, bronchitis, hay fever, sinusitis, parental asthma, and parental atopy. Neither bronchiolitis, eczema, croup, personal cigarette smoking, maternal smoking, paternal smoking, nor delivery complications bore an apparent relation to the development of asthma. A history of parental asthma or parental atopy did not significantly alter the sex-adjusted relative risk estimates for pneumonia, bronchitis, hay fever, or sinusitis. These results support the hypothesis that asthma is a multifactor disease whose expression is dependent on both familial and environmental influences.

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EARLY CHILDHOOD PREDICTORS OF ASTHMA

CHARLES B. SHERMAN,[1,2] TOR D. TOSTESON,[1] IRA B. TAGER,[3] FRANK E. SPEIZER,[1] AND SCOTT T. WEISS[1]

Sherman, C. B. (Pulmonary Div., The Miriam Hospital, Providence, RI 02906), T. D. Tosteson, I. B. Tager, F. E. Speizer, and S. T. Weiss. Early childhood predictors of asthma. *Am J Epidemiol* 1990;132:83–95.

To investigate potential risk factors for the development of childhood asthma, the authors undertook a longitudinal study using a cohort of 770 children aged 5–9 years from East Boston, Massachusetts, that has been under study since 1975. The disease outcome considered was age at first onset of asthma, as determined by parental or self-reporting of a physician's diagnosis. Potential risk factors were evaluated specifically in relation to their presence antecedent to a diagnosis of asthma. Standardized questionnaires were used to obtain childhood illness histories, environmental exposures, and the asthmatic and atopic statuses of first-degree relatives. Ninety-one cases of asthma were identified from 1975 to 1988 (57 males and 34 females). Significant sex-adjusted relative risk estimates were seen for antecedent pneumonia, bronchitis, hay fever, sinusitis, parental asthma, and parental atopy. Neither bronchiolitis, eczema, croup, personal cigarette smoking, maternal smoking, paternal smoking, nor delivery complications bore an apparent relation to the development of asthma. A history of parental asthma or parental atopy did not significantly alter the sex-adjusted relative risk estimates for pneumonia, bronchitis, hay fever, or sinusitis. These results support the hypothesis that asthma is a multifactor disease whose expression is dependent on both familial and environmental influences.

asthma; child; genetics; hypersensitivity; respiratory tract infections

A number of studies have been carried out to investigate risk factors for childhood asthma (1–16). Hospital-based and case-control studies have consistently shown that lower respiratory illness (1–6) and atopy (7–10) are associated with asthma in children. Available longitudinal and community-based studies have found associations between perinatal, social, infectious, and allergic exposures and the risk of asthma in children (11–16). Some uncertainty remains, however, as to the identity and causal significance of early childhood predictors for the development of asthma. The present investigation used longitudinal data from a cohort of 5- to 9-year-old chil-

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Abbreviations: FEF_{25-75}, forced expiratory flow from 25 percent to 75 percent of forced vital capacity; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

[1] Channing Laboratory, Department of Medicine, Harvard Medical School and Brigham and Women's Hospital, Boston, MA.

[2] Current address: The Miriam Hospital, Providence, RI.

[3] Veterans Administration Medical Center, University of California, San Francisco, CA.

Reprint requests to Dr. Charles B. Sherman, The Miriam Hospital, 164 Summit Avenue, Providence, RI 02906.

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dren with 13 years of follow-up to evaluate the importance of a range of potential risk factors whose assessment was made antecedent to the onset of asthma.

MATERIALS AND METHODS

Selection of study sample

Details of the characteristics of the study population have been published elsewhere (17). Briefly, a 34 percent random sample was selected from all children 5–9 years of age enrolled in public and parochial schools in East Boston, Massachusetts, in September 1974. Between January and June of 1975, interviewers visited the households of these children and enumerated all household residents. The residents together with the index children comprised the total study population. All members of the study population were screened annually beginning in 1975, with the exception of the second and third screenings (1976 and 1977). The 5- to 9-year-old index children and siblings of the same ages comprised the study population for these analyses. Data collected during the first year (1975) and for 11 consecutive years (1978–1988) were used.

Data collection

Standardized questionnaires were used to obtain data on respiratory symptoms and illnesses, cigarette smoking history, and household demographics. Questions relating to chronic respiratory symptoms were those proposed by the Division of Lung Diseases of the National Heart, Lung, and Blood Institute (18). At the first screening, separate but similar questionnaires were used for subjects aged less than 10 years and those aged 10 years or older. Beginning with the fourth screening cycle (September 1977–June 1978), a common questionnaire was used for all subjects. Parents answered all questions for children younger than 10 years of age, except for those questions that pertained to the child's smoking history, which were answered by the child during pulmonary function testing (when parents were not present). Children aged 10 or older answered all questions for themselves.

The time periods covered by these questionnaires differed. The initial questionnaire asked about events in the child's life prior to and up to entry into the study; the fourth year questionnaire focused on events for the period between study entry and the fourth year ("gap" years). Thereafter, each annual survey obtained information about events that occurred between annual surveys or between the time the subject was last seen and the current survey. The age at first occurrence of an illness was defined as the age (in years) at the time of the survey in which a positive response was recorded or the age (in years) at the time of the fourth survey for positive responses occurring during the "gap" years.

Ventilatory function was tested using an 8-liter, water-filled, portable recording spirometer (Survey spirometer; Warren Collins, Inc., Braintree, MA) with the subject in the sitting position and without the use of a nose clip. The spirometers were calibrated on a regular basis. Subjects were encouraged to perform FVC maneuvers until five acceptable tracings were obtained or until it became evident that they could not perform adequately. A tracing was considered acceptable if it was at least 4 seconds in duration and reached an asymptote of at least 1 second. All pulmonary function measurements were corrected to body temperature, ambient pressure, and saturation with water vapor at these conditions.

FVC, FEV_1, and FEF_{25-75} were obtained by standard technique (19). FVC, the greatest volume that can be forcefully exhaled from total lung expansion, may be reduced in subjects with restrictive or severe obstructive ventilatory defects. FEV_1 and FEF_{25-75}, measures of airflow, are reduced in obstructive lung diseases. When mean values of these measurements were used, they were obtained as the mean of the best three of five tracings, as recommended by

the Division of Lung Diseases (18). Mean lung function values were converted into percent predicted values using the nomograms of Dickman et al. (20).

The disease outcome for this investigation was age at first occurrence of a physician's diagnosis of asthma, as reported by the subject or his/her parent. Hay fever, sinusitis, eczema, pneumonia, and bronchitis were defined by the subject's or parent's report of a physician's diagnosis of these illnesses on the initial or yearly surveys. Smoking statuses of the index children and their parents were determined from the initial or yearly questionnaire responses. Croup and bronchiolitis were defined by the subject's or parent's report of a physician's diagnosis of these illnesses on the initial questionnaire. Age at first occurrence was obtained for these latter variables.

Other exposure variables included delivery complications, parental asthma, and parental atopy. Information on delivery complications ("Were there any problems with him/her at the time of delivery?"—yes or no) was available only on the initial questionnaire. A parental history of asthma was considered present if either parent of the index child reported, at any time during the study period, ever receiving a physician's diagnosis of the condition. Similarly, parental atopy was defined as self-reporting by either parent of a physician's diagnosis of hay fever and/or eczema at any time during the study period.

Follow-up and losses to follow-up

Asthmatics and nonasthmatics were followed for a comparable number of years (9.2 ± 3.0 (standard deviation) vs. 8.9 ± 3.5, respectively; $p = 0.44$). No sex differences in follow-up years were detected. Incident asthmatics, however, were followed for significantly more years than nonasthmatics (9.7 ± 2.5 vs. 8.9 ± 3.5, respectively; $p = 0.04$), possibly reflecting greater personal or parental concern about their illness.

Of the original 770 members of the cohort, 86 (11.2 percent) were lost to follow-up after the initial survey. At the initial survey, 81 of these subjects were identified as nonasthmatic (11.9 percent of 679 never asthmatics) and five subjects were identified as asthmatic (5.5 percent of 91 asthmatics).

Statistical analysis

The overall goal of the analysis was to identify risk factors for the onset of asthma whose occurrence antedated the time ("age") of first diagnosis of asthma. The Cox proportional hazards model with time-dependent covariates and age as the time variable was used for this purpose (21).

This method was selected because it 1) accounts for the variable length of follow-up time available for each subject and 2) permits the use of covariate data that can legitimately change from survey to survey. The second feature was used in the following way to evaluate the relative risk of first onset of asthma: For those childhood illnesses for which age at first occurrence was available, an age-dependent covariate was created with a value of 1 (exposed) for ages greater than the age at first occurrence of the illness and 0 (unexposed) for ages less than or equal to the age at first occurrence of illness. The procedure assured that any observed increase in risk must pertain to antecedent occurrence of the illness. For comparative purposes, a second age-dependent covariate was created with a value of 1 (exposed) for ages greater than or equal to the age at first occurrence of the illness. The observed increase in risk using this covariate pertained to an antecedent *or* concurrent exposure.

The application of the Cox model required determining the age of first onset of asthma, as well as the age of first occurrence of other childhood respiratory illnesses. These determinations were complicated somewhat by the pattern of administration of the questionnaire. In the first

year of the study, information concerning age of onset was requested whenever an occurrence of illness was reported. Thus, for ages of onset prior to entry into the study, there is a potential recall bias. This was investigated by introducing an age-dependent variable with a value of 1 for ages of onset at or following entry into the study and 0 for ages before entry, and by fitting interaction effects between this variable and the covariates of interest.

The questionnaire administered in the fourth year of the study did not request the age of onset for asthma and other illnesses occurring since the first year of the study. For illnesses occurring in this 2-year "gap," the age of onset was taken to be the age of the child at year 4 of the study. To examine the impact of this procedure, we performed analyses using 1) the age at year 1 of the study for both the covariate illnesses and asthma; 2) the age at year 1 of the study for the covariate illness with the age at year 4 for asthma; and 3) the reverse of the assignments in part 2.

Student's t tests (two-tailed) were used for comparison of mean spirometric values for asthmatics and nonasthmatics. Only the most recent spirometric lung function for each individual was used in the analysis. Chi-square statistics and Fisher's exact test (two-tailed) were used to test for associations between sex and use of medications and hospitalizations for asthmatics.

RESULTS

Characteristics of asthmatics

There were 91 subjects diagnosed as having asthma during the 13 years of the study. Forty-three asthmatics were diagnosed after entry into the study. Male asthmatics exceeded the expected number based on the sex distribution of the study population (asthmatics: 57 (62.6 percent) males and 34 (37.4 percent) females; study population: 402 (52.2 percent) males and 368 (47.8 percent) females; $p < 0.05$).

Asthmatics and nonasthmatics had normal ranges for all spirometric tests analyzed. All of these spirometric comparisons were performed using the most recently available spirometric lung function value for all individuals. Male asthmatics had larger FVC percent predicted values than male nonasthmatics (102.2 ± 1.7 (standard error of the mean) vs. 98.0 ± 0.8; $p = 0.02$), and female asthmatics had lower FEV_1 percent predicted values than female nonasthmatics (100.9 ± 3.1 vs. 110.3 ± 0.9; $p = 0.002$). No statistically significant difference was found for mean age at the time of most recent testing for asthmatics and nonasthmatics. Asthmatics were, however, taller than nonasthmatics at the last visit (63.4 ± 0.7 cm (standard error of the mean) vs. 61.6 ± 0.3 cm, respectively; $p = 0.04$).

Two analyses were undertaken to evaluate the severity of disease in the asthmatics. Asthmatics diagnosed by the first survey (prevalent cases, $n = 48$) were traced in years 4–13 of the study to determine the frequency of a physician's diagnosis of active asthma. Of these 48 prevalent cases, 13 (27.1 percent) reported an asthmatic diagnosis at least once in the 10-year follow-up. As determined by questionnaire, four of the 91 asthmatics (4.4 percent) were hospitalized at the age of asthma occurrence and nine of the total group (9.9 percent) were ever hospitalized for asthma during the 11 subsequent years of the study. A mean of 1.6 ± 1.0 (standard deviation) hospital admissions for asthma was recorded for those hospitalized. Of the female cases, 17.7 percent ($n = 6$) were hospitalized at least once compared with 5.3 percent of the male cases ($n = 3$) ($p = 0.07$). Fifty-six of the cases (61.5 percent) were medicated for asthma at some time during the follow-up period; the mean number of surveys at which medication use was reported among these children was 3.4 ± 2.5 (standard deviation). Females reported having ever used medication (67.6 percent, $n = 23$) more often than males (57.9 percent, $n = 33$), but the difference was not statistically significant.

Risk factors

The occurrence or presence, at any time during the study, of respiratory illnesses, atopy, personal or secondary cigarette smoke, delivery complications, parental asthma, and parental atopy is shown in table 1 for asthmatics and nonasthmatics. Asthmatics more frequently reported pneumonia, bronchitis, hay fever, sinusitis, parental asthma, and parental atopy than nonasthmatics. Prevalent and incident asthmatics had similar occurrences of these factors except hay fever, which was found more often in incident asthmatics than in prevalent asthmatics ($n = 26$ (60.5 percent) vs. $n = 16$ (33.3 percent); $p = 0.01$). At the time of entry into the study, prevalent and incident asthmatics had comparable occurrences of these factors (data not shown).

Sex-adjusted relative risks of asthma associated with these antecedent exposures are presented in table 2. Significant relative risk estimates were found for pneumonia, bronchitis, hay fever, sinusitis, parental asthma, and parental atopy. All other factors studied bore no apparent relation to the development of asthma (table 2). Although the sex-adjusted relative risk estimate associated with personal smoking did not reach statistical significance, it was of the same magnitude as the other significant estimates. Small numbers may explain the lack of statistical significance. Analyses that used antecedent and antecedent-concurrent covariates produced comparable results. Only antecedent covariates were used in analyses to explore possible causal relations.

Effect modification by illness onset before or after entry into the study was analyzed to evaluate potential recall bias. No statistically significant interaction by time

TABLE 1

Potential risk factors for asthma in a longitudinal study of 770 children aged 5–9 years, East Boston, Massachusetts, 1975–1988

Factor	Prevalent asthma ($n = 48$) No. (%)	Incident asthma ($n = 43$) No. (%)	Nonasthmatics ($n = 679$) No. (%)	p
Lower respiratory illness				
Pneumonia	18 (37.5)	18 (41.9)	91 (13.4)	≤0.001
Bronchitis	20 (41.7)	20 (46.5)	121 (17.8)	≤0.001
Bronchiolitis	—*	1 (2.3)	8 (1.2)	0.59
Atopy				
Hay fever	16 (33.3)	26 (60.5)	108 (15.9)	≤0.001
Eczema	6 (12.5)	9 (20.9)	73 (10.8)	0.12
Upper respiratory illness				
Sinusitis	14 (29.2)	20 (46.5)	100 (14.7)	≤0.001
Croup	5 (10.4)	9 (20.9)	96 (14.1)	0.34
Other factor				
Personal cigarette smoking	10 (20.8)	14 (32.6)	135 (19.9)	0.14
Maternal smoking	34 (70.8)	27 (62.8)	431 (63.5)	0.58
Paternal smoking	26 (54.2)	24 (55.8)	395 (58.2)	0.83
Delivery complications	8 (16.7)	8 (18.6)	92 (13.8)	0.60
Familial factor				
Parental asthma	19 (39.6)	20 (46.5)	178 (26.2)	0.003
Parental atopy	31 (64.6)	31 (72.1)	367 (54.0)	0.03

* No occurrence.

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TABLE 2

Sex-adjusted relative risk of asthma associated with various factors in a longitudinal study of 770 children aged 5–9 years, East Boston, Massachusetts, 1975–1988

Factor	Antecedent exposure		Antecedent, concurrent exposure	
	Sex-adjusted relative risk	95% confidence interval	Sex-adjusted relative risk	95% confidence interval
Lower respiratory illness				
Pneumonia	3.77	2.29–6.20	4.42	2.83–6.91
Bronchitis	2.66	1.64–4.31	3.22	2.09–4.97
Bronchiolitis	—*	—*	—*	—*
Atopy				
Hay fever	4.44	2.17–9.08	8.17	4.56–14.64
Eczema	1.39	0.67–2.91	1.68	0.89–3.17
Upper respiratory illness				
Sinusitis	3.60	1.74–7.44	4.33	2.30–8.17
Croup	0.88	0.36–2.16	0.99	0.45–2.14
Other factor				
Personal cigarette smoking	2.29	0.67–7.88	2.82	0.98–8.09
Maternal smoking	1.09	0.68–1.74	1.18	0.76–1.83
Paternal smoking	1.20	0.62–2.31	1.14	0.63–2.06
Delivery complications	1.27	0.74–2.19		
Familial factor				
Parental asthma	1.95	1.29–2.95		
Parental atopy	1.61	1.03–2.50		

* No occurrence.

of entry was found (data not shown). Pneumonia, bronchitis, hay fever, sinusitis, parental asthma, and parental atopy remained the only significant sex-adjusted predictors detected. In addition, the effect of interval assignment for the onset of covariate illnesses and asthma occurring in the "gap" years was analyzed. No significant differences in relative risk estimates for the occurrence of asthma by interval assignments were found (data not shown). Therefore, all further analyses were performed by assigning illness onset in the "gap" years as the age of the child at year 4 of the study.

A proportional hazards model was constructed that included the six sex-adjusted covariates that were found to be significantly associated with asthma (table 3). Bronchitis, hay fever, and parental asthma were the only significant predictors after adjusting for sex and other covariates in the model. Based upon the estimated covariances of the parameter estimates, the correlation between the coefficients was −0.39 for pneumonia and bronchitis, −0.30 for hay fever and sinusitis, and −0.23 for parental asthma and parental atopy.

TABLE 3

Relative risk of asthma associated with significant environmental and familial factors, as estimated by multiple regression, in a longitudinal study of 770 children aged 5–9 years, East Boston, Massachusetts, 1975–1988

Factor	Relative risk	95% confidence interval
Sex (male/female)	2.39	1.35–4.23
Pneumonia (yes/no)	1.38	0.67–2.88
Bronchitis (yes/no)	3.62	1.94–6.77
Hay fever (yes/no)	2.92	1.20–7.08
Sinusitis (yes/no)	2.21	0.88–5.52
Parental asthma (yes/no)	2.43	1.38–4.29
Parental atopy (yes/no)	1.44	0.84–2.48

Figure 1 graphically illustrates the importance of selected predictors to the cumulative incidence of asthma, by age, using parameter estimates from the full data set. Panel A shows the unadjusted Kaplan-Meier estimates (22) of the cumulative incidence function for the cohort. In this plot, 10.6 percent of the population is shown to have developed asthma by age 12. Based on the adjusted model presented in table 3 and assuming no identified risk factors, males had a greater cumulative incidence of asthma than did females by this age (7.2 percent vs. 3.1 percent; panel B). Furthermore, 23.8 percent of males with bronchitis before age 1 but no other risk factors and 10.8 percent of females with a similar respiratory history had asthma by age 12 (panels C and D).

The possibility that sex altered the associations of the individual risk factors and asthma was evaluated (table 4). Females had a greater risk for the occurrence of asthma associated with all individual risk factors except for bronchitis. Statistical significance, however, was detected only for this interaction of sex and parental asthma and atopy.

Two additional analyses were performed to examine the plausibility of a causal relation between asthma and other illnesses. First, four proportional hazards models were constructed that used bronchitis, pneumonia, hay fever, and sinusitis, respectively, as the dependent variable with asthma as one of the independent covariates (table 5). If significant relations were seen in these "reversed" models, it

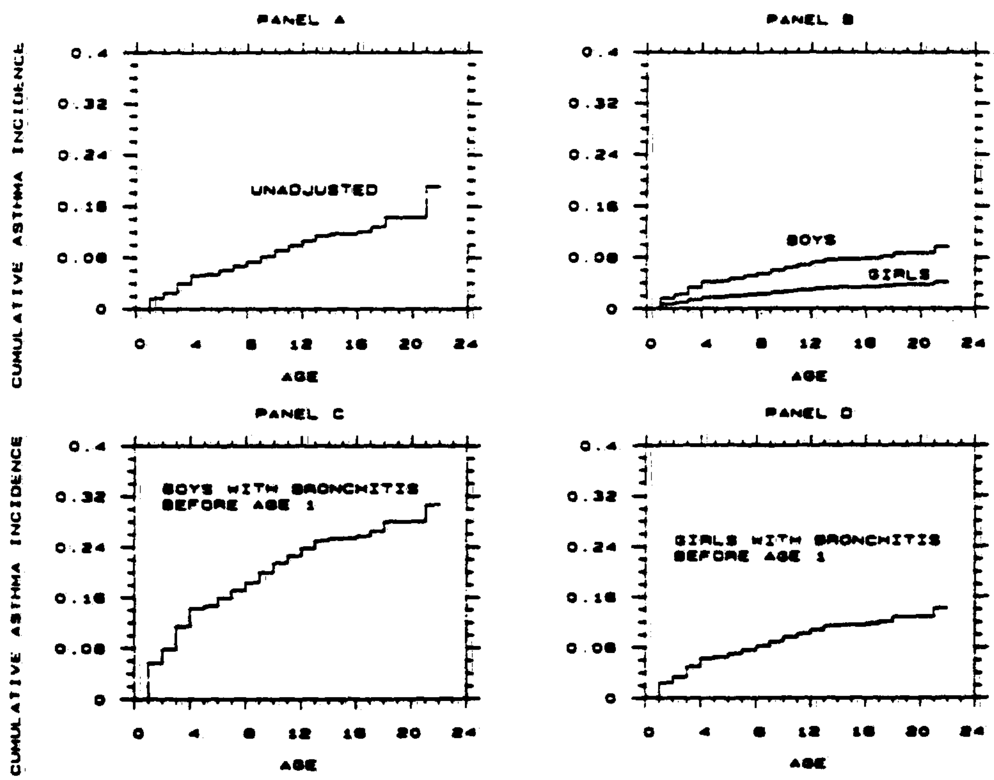

FIGURE 1. Cumulative incidence of asthma, by age, in a longitudinal study of 770 children aged 5-9 years, East Boston, Massachusetts, 1975-1988. Panel A, incidence unadjusted for risk factors; Panel B, incidence for children with no risk factors, by sex; Panels C and D, incidence for children who had bronchitis before age 1 year but no other risk factors.

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would suggest that asthma and the illnesses were occurring at about the same time in childhood, rather than sequentially as in a causal model. Asthma was not identified as a significant covariate in models that defined bronchitis or pneumonia as the outcome variable, but it was a statistically significant risk factor for hay fever and sinusitis (table 5).

In the second analysis, simple cross-tabulations were prepared showing the temporal relations between age of onset of asthma and other illnesses for those individuals who developed both. More subjects had the occurrence of bronchitis ($n = 25$ vs. $n = 7$) and pneumonia ($n = 22$ vs. $n = 7$) before, rather than after, the occurrence of asthma, whereas twice as many subjects had the occurrence of hay fever ($n = 11$ vs. $n = 22$) and sinusitis ($n = 10$ vs. $n = 20$) after and not before the occurrence of asthma. Additionally, bronchitis was a significant risk factor for the development of pneumonia, while hay fever and sinusitis were both significant predictors of each other (data not shown). This analysis would suggest that bronchitis and pneumonia as well as hay fever and sinusitis are indistinguishable from one another as predictors.

The risk of asthma associated with any of the individual covariates did not vary by parental asthma or parental atopy (data not shown). However, several interesting trends were seen. The risk of asthma was greatest in subjects with hay fever or sinusitis if they had parental asthma and in subjects with bronchitis or pneumonia if they did not have parental asthma. Additionally, the risk of asthma was greatest in subjects with pneumonia or bronchitis if they had parental atopy.

The effect of age at first occurrence of asthma (age <10 years or ≥10 years) on the relations of the individual risk factors and asthma was assessed (data not shown). This age categorization was chosen because parents answered all questions for children younger than 10 years of age. Again, no

TABLE 4

Interaction of sex and significant environmental and familial factors for asthma in a longitudinal study of 770 children aged 5–9 years, East Boston, Massachusetts, 1975–1988

Factor	Relative risk		p
	Male	Female	
Environmental factor			
Pneumonia (yes/no)	3.03	3.85	0.63
Bronchitis (yes/no)	4.23	2.46	0.35
Hay fever (yes/no)	2.37	4.80	0.24
Sinusitis (yes/no)	1.73	3.83	0.24
Familial factor			
Parental asthma (yes/no)	0.52	3.13	0.0002
Parental atopy (yes/no)	0.57	3.02	0.014

TABLE 5

Sex-adjusted relative risk of upper and lower respiratory illnesses associated with asthma in a longitudinal study of 770 children aged 5–9 years, East Boston, Massachusetts, 1975–1988

Dependent variable	Independent covariates	Relative risk	95% confidence interval
Bronchitis	Sex (male/female)	1.14	0.84–1.56
	Asthma (yes/no)	2.08	0.95–4.51
Pneumonia	Sex (male/female)	1.11	0.78–1.58
	Asthma (yes/no)	1.93	0.88–4.21
Hay fever	Sex (male/female)	1.03	0.74–1.43
	Asthma (yes/no)	2.64	1.66–4.18
Sinusitis	Sex (male/female)	1.19	0.84–1.70
	Asthma (yes/no)	2.18	1.34–3.54

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statistically significant difference was found by age of first occurrence of asthma for the relations of any of the individual covariates and asthma. However, point estimates for hay fever and sinusitis were larger before age 10 (9.46 vs. 3.06 and 4.95 vs. 3.10, respectively), while point estimates for bronchitis and pneumonia were greater at or after age 10 (2.46 vs. 2.97 and 3.69 vs. 3.87, respectively).

Discussion

This investigation focused on the quantitative effects of a number of factors that are thought to be associated with and possibly causally related to the occurrence of asthma. Unlike many previous studies, it paid special attention to the temporal relation of the potential risk factors and the occurrence of asthma. The cohort of study children, 5- to 9-year-olds at intake, came from a stable, relatively homogeneous population. The self-report of a physician's diagnosis of asthma determined disease outcome. The asthmatics so identified in this study were similar to other previously described school-aged asthmatics (5, 6, 11–16). They were diagnosed at a young age and had reduced FEV_1 and FEF_{25-75} percent predicted values compared with the nonasthmatics (5, 13, 23). The severity of disease was mild, as is documented by the findings that only 9.9 percent of the asthmatic group were ever hospitalized and 61.5 percent were ever medicated in the 13 years of the study. Most of the prevalent asthmatics (62.5 percent) did not report a further diagnosis of asthma, which is in close agreement with the 65.9 percent rate reported in the National Child Development Study (11) and the 70 percent rate reported from Australia by McNicol and Williams (13).

Sex differences were evident in the asthmatic group. More males than females reported a diagnosis of asthma. Additionally, males were diagnosed more frequently at younger ages and had less extreme disease, as measured by fewer hospitalizations recorded. Clear male/female differences were evident for the effect of asthma on lung function level. Male asthmatics had larger FVC percent predicted and female asthmatics had lower FEV_1 percent predicted than their counterparts. Thus, even after adjusting for differences in height and age, there were male/female differences in level of lung function. The meaning of these differences is unclear and requires further investigation.

The results support the hypothesis that asthma is a multifactor disease whose expression is dependent on both familial and environmental influences. The exact mode of genetic transmission for asthma is still unknown. Autosomal dominance with incomplete penetrance (24) and polygenic inheritance (25) are thought to be the most likely modes of genetic expression. This study was not designed to evaluate specific genetic pathways, but the findings do provide some insight into the interplay between atopy and asthma in first-degree relatives and the development of asthma in childhood. Parental asthma and atopy were both significant bivariate predictors for childhood asthma, which reaffirms the observation that asthma clusters in families (26) and can be inherited as part of a general allergic susceptibility (27, 28). Parental asthma was a stronger predictor than parental atopy, a finding that agrees with previous studies that have shown that parental atopy may enhance the likelihood for the expression of asthma but does not, on its own, impart as great a risk as does parental asthma (25, 29, 30). These data suggest that inheritance of asthma and atopy overlap but are not identical. Females were more likely to develop asthma than males if they had a parental history of asthma or atopy. The significance of this finding is unclear and requires further research.

Four antecedent respiratory illnesses increased the risk of asthma in childhood. Bronchitis, pneumonia, hay fever, and si-

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nusitis all showed significant sex-adjusted relative risk estimates. Bronchitis and hay fever were the most important predictors detected after adjusting for the effects of the other individual covariates. This result, however, must be interpreted with caution, since bronchitis and pneumonia or hay fever and sinusitis are often clinically indistinguishable from each other. Furthermore, bronchitis was predictive of pneumonia and hay fever and sinusitis were each predictive of the other in the Cox models, indicating a high correlation between these variables.

The mechanisms by which bronchitis, hay fever, pneumonia, or sinusitis may cause asthma remain speculative. Bronchitis may act directly by inducing structural changes in the airways (31) or causing alterations in autonomic control of smooth muscle tone (32, 33), leading to increased levels of airway responsiveness and hence to the onset of asthma. In the study population, asthma occurred more often after bronchitis and was not a significant predictor for the occurrence of this illness. Both of these findings would support a possible direct mechanism. A direct pathway for hay fever is less feasible, but indirect mechanisms can be postulated. Hay fever may alter breathing patterns and allow more sensitizing agents (e.g., cold air, aeroallergens) access to the airways, which in turn may increase asthma expression. Alternatively, subjects with a tendency to develop hay fever may also be at risk for developing asthma. Asthma occurred more often before hay fever and was a significant predictor for the occurrence of hay fever. Thus, a direct biologic pathway may be responsible for the development of asthma in nonatopic subjects, while an indirect pathway may be operating in atopic children (34). This hypothesis requires further testing, however, since no direct measures of atopy (i.e., skin testing, immunoglobulin E levels) were obtained in this investigation. Diagnostic misclassification may explain the significance of pneumonia and sinusitis as risk factors for the occurrence of asthma. Of course, subjects with these illnesses may also be indirectly at risk for developing asthma.

A familial predisposition for asthma did not influence the associations between significant covariate predictors and the onset of asthma. Low study power and crude inheritance markers may explain this finding. It is interesting, nonetheless, to examine the parameter estimates from this analysis. Bronchitis had a much greater effect on the development of asthma in subjects without parental asthma. This again supports the concept that injury to the airways, in and of itself, may be sufficient to cause asthma. Hay fever was a stronger predictor in individuals with parental asthma, implying that the expression of asthma and atopy may be interrelated.

Many infectious and environmental factors were not predictive of asthma. It is noteworthy that bronchiolitis and croup were not found to be significant predictors of asthma in this study. These results contrast with those of previously reported studies (3, 4, 9, 35). This finding may reflect a lower occurrence rate and/or a milder expression of these diseases in the East Boston community compared with the other groups studied. An additional possibility is that croup and bronchiolitis are collinear with pneumonia and bronchitis. Alternatively, these respiratory illnesses occurring early in life may be of relevance only for asthma onset at an early age, and the study may lack sufficient power to detect this. Delivery complications had little effect on the risk of asthma and may indicate the imprecise measurement of this variable.

None of the cigarette smoking variables were predictive of asthma. Parental smoking may have resulted in exposure levels too low to increase the risk of asthma. This seems unlikely given previous findings of the relation of parental smoking to wheezing symptoms in children and reduced levels of lung function in asthmatic children (36). Another possible explanation is that

parental smoking may be not causal but a modifier of the severity of asthma in children with this disorder. In addition, parents in households with wheezing children may have altered their smoking habits. A self-selection factor may explain the lack of significance for personal smoking. Children with hyperresponsive airways may not be able to tolerate the irritating effects of tobacco smoke. Additionally, the low prevalence of personal smoking in this age group may have resulted in reduced statistical power.

Asthma remains a disease that defies definition partially because of the heterogeneity of clinical expression. A self-report of a doctor's diagnosis of asthma, as obtained from a standardized questionnaire, is widely used to identify persons with asthma for epidemiologic research (37–39). Nonetheless, in children, using this definition may result in underdiagnosis of asthma. Taussig et al. (40) concluded from a study of the diagnostic criteria used by Tucson clinicians that considerable overlap of chronic bronchitis and asthma existed. Furthermore, Speight et al. (41) found that asthma was diagnosed in only a small proportion of English schoolchildren with a history of wheezing and bronchial responsiveness to histamine. To the extent that underreporting has occurred in this study, estimates of relative risk for asthma are conservative and are biased toward the null value. A similar argument can be made for self-reporting of a doctor's diagnosis of the other upper and lower respiratory illnesses studied.

Current concepts of asthma as a disease incorporate measures of bronchial hyperresponsiveness. Nonspecific airways responsiveness to cold air challenge has been assessed in a subset of the asthmatics used in these analyses. In a cross-sectional study, Weiss et al. (42) found that 11 of 12 asthmatics with any wheezing in the study year had increased bronchial responsiveness using a cutoff value for cold air challenge of a greater than 9 percent decrease in prechallenge FEV_1/FVC. The one asthmatic not responding had a borderline 8 percent decrease in FEV_1/FVC. Increased responsiveness was also significantly associated with a history of previous asthma. Thus, in this population, the definition of asthma appears to be very sensitive.

The study was designed to avoid several potential biases. Selection bias was not evident, as community and not hospital- or physician-referred participants were enrolled in the study. Preferential recall bias could have been present for those asthmatics diagnosed before entry into the study. Asthmatics or their parents may have been more likely to recall previous respiratory or atopic illnesses at the initial survey. It is unlikely, however, that this could explain our findings, since no effect modification by illness onset before or after study entry was detected. Physicians in the study community could have been more likely to diagnose a child as asthmatic given a parental history of asthma or atopy and frequent episodes of bronchitis, pneumonia, hay fever, or sinusitis. This potential bias could not be directly evaluated.

Associations found in this study met most of the standard epidemiologic criteria for causality (43, 44). An appropriate time sequence of cause before effect was assured by the study definition of exposure and by the use of time-dependent covariates in the analyses. The study results demonstrated consistency with replication. Risk factors for asthma identified by these analyses were similar to those found by several other community-based studies (11–16). Strong associations were found, as is seen by the large relative risk parameter estimates for the significant covariates. The strength of these associations would suggest that bias is less likely to explain the findings. Asthma is a multifactor disease, and therefore specificity of association would not be expected to be upheld. Dose-response relations were not evaluated, and biologic coherence, as previously discussed, remains speculative but plausible.

In conclusion, several risk factors for the development of childhood asthma have been identified. This study improved upon the methodology used in other population-based studies by ensuring antecedent exposures and by minimizing the effects of selection bias and preferential recall bias.

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Weitzman, M., Gortmaker, S., Walker, D.K., Sobol, A. "Maternal Smoking and Childhood Asthma" Pediatrics 85(4): 505-511, 1990.

ABSTRACT. According to a substantial literature, passive smoking by children is associated with an increased incidence of lower respiratory illness and diminished pulmonary function. The relationship between passive smoking and childhood asthma, however, is not clear. Data from the Child Health Supplement to the 1981 National Health Interview Survey were analyzed with information about 4331 children aged 0 to 5 years to study the relationship between maternal smoking and (1) the prevalence of childhood asthma, (1)[sic] the likelihood of taking asthma medication, (3) the age of onset of children's asthma, and (4) the number of hospitalizations among children with and without asthma. An odds ratio for asthma of 2.1 was shown by multivariate logistic regressions among children whose mothers smoke 0.5 packs of cigarettes or more per day compared with children of nonsmokers (P=.001). In similar analyses maternal smoking of 0.5 packs per day was identified as an independent risk for children's use of asthma medications (odds ratio 4.6, P=.0006) and for asthma developing in the first year of life (odds ratio 2.6, P=.0006). Maternal smoking is also associated with increased numbers of hospitalizations by its association with an increased risk of asthma as well as by contributing to hospitalizations independently of a child having asthma. Among children with asthma, however, maternal smoking is not associated with increased numbers of hospitalizations. It was concluded that maternal smoking is associated with higher rates of asthma, an increased likelihood of using asthma medications, and an earlier onset of the disease. These findings have implications for renewed efforts to discourage smoking in families, especially during pregnancy and the first 5 years of children's lives.

Maternal Smoking and Childhood Asthma

Michael Weitzman, MD; Steven Gortmaker, PhD; Deborah Klein Walker, EdD; and Arthur Sobol, MA

From the Department of Pediatrics, Boston City Hospital and Boston University School of Medicine, the Boston University School of Public Health, and the Harvard School of Public Health, Boston, Massachusetts

ABSTRACT. According to a substantial literature, passive smoking by children is associated with an increased incidence of lower respiratory illness and diminished pulmonary function. The relationship between passive smoking and childhood asthma, however, is not clear. Data from the Child Health Supplement to the 1981 National Health Interview Survey were analyzed with information about 4331 children aged 0 to 5 years to study the relationship between maternal smoking and (1) the prevalence of childhood asthma, (1) the likelihood of taking asthma medication, (3) the age of onset of children's asthma, and (4) the number of hospitalizations among children with and without asthma. An odds ratio for asthma of 2.1 was shown by multivariate logistic regressions among children whose mothers smoke 0.5 packs of cigarettes or more per day compared with children of nonsmokers (P = .001). In similar analyses maternal smoking of 0.5 packs per day was identified as an independent risk for children's use of asthma medication (odds ratio 4.6, P = .0006) and for asthma developing in the first year of life (odds ratio 2.6, P = .0006). Maternal smoking is also associated with increased numbers of hospitalizations by its association with an increased risk of asthma as well as by contributing to hospitalizations independently of a child having asthma. Among children with asthma, however, maternal smoking is not associated with increased numbers of hospitalizations. It was concluded that maternal smoking is associated with higher rates of asthma, an increased likelihood of using asthma medications, and an earlier onset of the disease. These findings have implications for renewed efforts to discourage smoking in families, especially during pregnancy and the first 5 years of children's lives. *Pediatrics* 1990;85:505-511; *maternal smoking, asthma, passive smoking.*

The contribution of cigarette smoke to indoor air pollution[1] and the adverse health consequences of passive smoking[2-5] have recently come to be recognized as major public health problems. Estimates vary, but children living in temperate climates spend 60% to 80% of their time indoors[6] and approximately 70% of all children in the United States live in homes where there is at least one adult smoker.[5,7] According to a growing literature, increased childhood respiratory symptoms and altered respiratory function are associated with parental smoking. In general, it has been found in these studies that maternal smoking is more strongly correlated with children's respiratory dysfunction than is paternal smoking.[5-13] The most frequently offered explanations for this finding are that fathers spend less time at home than do mothers and that children spend more time with their mothers than their fathers. Hence, children are more likely to be exposed to passive smoke if their mothers smoke than if their fathers smoke. In at least two recent articles, however, it was suggested that maternal smoking during pregnancy may have independent effects on children's pulmonary structure and function.[14,15]

Among preschool children, the finding most frequently documented to date is an increased rate of lower respiratory infection and respiratory symptoms in children less than 2 years of age whose mothers smoke.[12,13,16-18] In most studies this association was shown to weaken or disappear as children grow older.[12,16-18] It was demonstrated in a further series of studies that maternal smoking is associated with diminished lung size[19] and decreased pulmonary function as measured by forced expiratory volume in 1 second, forced vital capacity, or forced expiratory flow, mid-expiratory phase among older children, thus suggesting long-term negative effects on children's pulmonary function.[5-11,20-26]

Although the consensus of the literature is that passive smoking is harmful to children, the rela-

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Reprint requests to (M.W.) HOB 421, Boston City Hospital, 818 Harrison Ave, Boston, MA 02118.

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tionship between parental smoking and the prevalence and severity of childhood asthma remains unclear. There are few studies of childhood asthma and maternal smoking in which large population-based data sets were used, and none that we are aware of in which a nationwide sample was used. Previous studies have been fairly evenly divided between those in which an increased prevalence of childhood asthma or chronic wheeze associated with parental smoking[8,10,22,27-29] was demonstrated and those in which it was not.[12,16,30-34]

We analyzed data from the Child Health Supplement to the 1981 National Health Interview Survey to study the relationship between maternal smoking and (1) the prevalence of childhood asthma among children aged 0 to 5 years, (2) the likelihood of taking asthma medications prescribed by a physician, (3) the age of onset of children's asthma, and (4) the numbers of overnight hospitalizations.

METHODS

In the National Health Interview Survey, a complex, multistage probability sampling design was used to provide a representative sample of the civilian noninstitutionalized population of the United States. In the 1981 survey there was a Child Health Supplement in which data were collected concerning one randomly chosen child in each eligible household. The supplement included 15 416 children aged birth to 17 years, of whom 4331 were aged 0 to 5 years, and contained data concerning maternal smoking. All information was derived from parent reports; there were no medical examinations of children or reviews of medical records. The interview contained a series of questions concerning family sociodemographic characteristics and a list of 59 chronic health conditions, including asthma, that children might have. Parents were asked if the index child had ever had asthma, if the asthma lasted for at least 3 months, whether the child still had asthma or if it has been cured, and how old the child was when asthma was first noticed. Children were categorized as having asthma if their parents reported that it was present at the time of the interview, had been present for more than 3 months, and had not been cured. Parents were also asked a series of questions about the age of the child at onset of asthma. In a separate series of questions, parents were asked whether the child had taken an asthma medication prescribed by a physician in the past 2 weeks. Children reported as having taken such medication for asthma were categorized as current users of asthma medications.

Questions were also asked about maternal smoking during pregnancy for all sample children aged 0 to 5 years. In other studies it has been indicated that women who smoke during pregnancy tend to continue to smoke following pregnancy.[35] Thus, the measure of maternal smoking used in these analyses includes both prenatal and postnatal exposure. No questions were asked about paternal smoking.

In previous studies[36,37] it was found that parent reports tend to overestimate the prevalence of clinically diagnosed chronic conditions; however, this overreporting tends to decline with the severity or perceived stigma of the conditions. The majority of population-based studies of childhood asthma have relied on parent reporting for the identification of children with asthma. Some authors[38] believe that exclusive dependence on physician reporting results in significant underreporting of childhood asthma. In one study[38] 96% of school-aged children with asthma could be identified by parent reporting, in another[39] parent reports of children's asthma were confirmed in 94% of patients,[39] and in another[40] it was shown that parent reports of childhood asthma are a good indicator of impaired ventilatory function.

Statistical Analysis

All survey responses were weighted when we calculated means and proportions using the weights provided by the National Center for Health Statistics, which reflect the probability of selection, nonresponse, and poststratification adjustments. *T* tests were used to evaluate differences in means and χ^2 tests were used to measure differences in proportions. Logistic regressions were also estimated when the dependent variable was dichotomous using the PC SAS CATMOD program. The coefficient estimates can be interpreted as odds ratios associated with the predictor variable. Multivariate linear regressions were used when the dependent variable was the number of overnight hospitalizations.

Estimates of statistical significance were made assuming simple random sampling. The actual sampling design was stratified, multistage, and clustered, and the assumption of simple random sampling in this case will result in overestimates of statistical significance. We expect that design effects will be as great as 1.5. For this reason, we only discuss associations significant at the .01 level or less.

RESULTS

As shown in Table 1, 26% of children's mothers reported smoking during pregnancy. Of these, 13% smoked less than a half-pack of cigarettes per day and 13% smoked a half-pack or more per day. Rates

and intensity of maternal smoking were substantially different for different subsets of women. Less educated women and women who report lower incomes were more likely to smoke and were more likely to smoke a half-pack of cigarettes or more per day than were more educated or more affluent women.

Asthma was reported as being present in 2.3% of children whose mothers did not smoke, 2.6% of children whose mothers smoked less than a half-pack of cigarettes per day, and 4.8% of children whose mothers smoked a half-pack or more per day ($P = .001$, Table 2). In Table 3, the relative odds ratio for asthma among children aged 0 to 5 years is shown according to maternal smoking behavior. Compared with mothers who did not smoke, the odds ratio for children whose mothers smoked less than a half-pack per day is 1.1 and the comparable ratio for children whose mothers smoked a half-pack of cigarettes or more per day is 2.1 ($P = .001$). When we used a multivariate analysis with a logistic regression model controlling for sex, race, presence

TABLE 1. Maternal Smoking During Pregnancy, 1981 National Health Interview Survey (n = 4636)*

	No. of Mothers	No Smoking	Smoke <½ Pack Day	Smoke ≥½ Pack Day
Race				
Black	632	74	18	8
White	3555	73	13	14
Other	144	90	9	••
Family income ($)				
<10,000	1053	64	19	17
10 000–25 000	1868	75	13	12
25 000+	1139	80	9	10
Maternal education				
<High school	1033	62	19	19
High school	1930	71	15	14
Some college	756	84	9	7
College	596	92	5	3
All children	4331	74	13	13

* Sample sizes will vary becaue of missing data. Results are given as percentages.
+ Estimate not reported because number in cell is less than five observations.

TABLE 2. Prevalence of Asthma and Current Use of Asthma Medications Among Children Aged 0 to 5 Years by Maternal Smoking Status, 1981 National Health Interview Survey (n = 4331)

Maternal Smoking Status	No. of Mothers	Prevalence of Asthma (%)	P Value	% of Children Currently Using Asthma Medications	P Value
No maternal smoking	3210	2.3		0.5	
Maternal smoking <½ pack/d	574	2.9	.68	*	
Maternal smoking ≥½ pack/d	547	4.8	.001	2.0	.0003
All children	4331	2.7		0.7	

* Estimate not reported because number in cell is less than five observations.

TABLE 3. Relative Odds Ratio for Asthma and Current Use of Asthma Medications Among Children Aged 0 to 5 Years by Maternal Smoking Status, 1981 National Health Interview Survey (n = 4331)

Maternal Smoking Status	Bivariate Analysis				Multivariate Analysis*			
	Asthma	P Value	Use of Asthma Medication	P Value	Asthma	P Value	Use of Asthma Medication	P Value
No maternal smoking	1.0		1.0		1.0		1.0	
Maternal smoking <½ pack/d	1.1	.68	+		1.2	.55	+	
Maternal smoking ≥½ pack/d	2.1	.001	4.1	.0003	2.1	.005	4.7	.0006

* Control variables include sex, race, presence of both parents, family size, and number of rooms in household.
+ Estimate not reported because number in cell is less than five observations.

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of both biologic parents, family size, number of rooms in household, and maternal education, the odds ratios are 1.2 and 2.1, respectively ($P = .005$, Table 3). Family income did not add significantly to this equation at $P < .05$.

We examined the relationship between maternal cigarette smoking and the prevalence of children reported as using a physician-prescribed asthma medication in the past 2 weeks. Overall, 7 per 1000 children 0 to 5 years of age were reported to be using asthma medications. The prevalence of asthma medication use was strongly associated with maternal smoking: the odds of a child using asthma medication was 4.1 times greater if the mother smoked a half-pack or more of cigarettes per day compared with nonsmokers ($P = .0003$, Table 3). When multivariate controls were introduced to control for potential confounding variables, the odds ratio was 4.7 ($P = .0006$). Control variables included sex, race, presence of both biologic parents, family size, number of rooms in the household, and maternal education. Family income did not add explanatory power to this equation.

We also estimated the association between cigarette smoking of the mother and the reported onset of asthma in the first year of the child's life. The prevalence of onset of asthma in the first year of life was 4.5% if the mother smoked a half-pack or more per day and 1.6% if she did not smoke ($P = .0001$). Multivariate logistic regressions indicated an odds ratio of 2.6 if the mother smoked a half pack or more of cigarettes per day ($P = .0006$, Table 4).

Because of concern that parents might mistakenly report respiratory illnesses associated with wheezing as asthma among children less than 2 years of age, we investigated the relationship between maternal smoking and asthma and use of asthma medications among children aged 2 to 5 years. With multivariate analyses, again controlling for sex, race, presence of both biologic parents, family size, number of rooms, and maternal education, we saw an odds ratio of 1.9 for asthma ($P = .003$) and 3.6 for the use of asthma medications ($P = .01$) for children whose mothers smoke a half-pack of cigarettes or more per day compared with children whose mothers do not smoke.

We also examined the reported number of overnight hospitalizations among children and their relationship to maternal smoking. There was a strong relationship of hospitalizations to maternal smoking (Figure). For children without asthma this relationship was highly statistically significant ($P = .0001$) and changed little when controls for socioeconomic variables were introduced. For the children with asthma, the relationship between maternal smoking and number of hospitalizations was not statistically significant.

DISCUSSION

These data from the population-based Child Health Supplement to the 1981 National Health Interview Survey indicate that maternal cigarette smoking is associated with higher rates of asthma, an increased likelihood of using asthma medications, and an earlier onset of the disease among children 0 to 5 years of age, independent of a number of other potentially confounding variables. Children whose mothers smoke one half-pack of cigarettes or more per day are twice as likely to have asthma and are four times as likely to use asthma medications as are children whose mothers do not smoke. The data also demonstrate that 26% of American children live in households with mothers who report smoking during pregnancy. Currently 26% of American adults smoke (*Time*, April 18, 1988:71-90); thus, rates of prenatal and early childhood passive exposure to maternal cigarette smoke are comparable with rates of active smoking among adults in the United States.

All information in this study is based on parent reports of asthma and smoking; hence, the results should be interpreted with some caution. Questions

TABLE 4. Relative Odds Ratio for Onset of Asthma in the First Year of Life by Maternal Smoking Status, 1981 National Health Interview Survey (n = 4331)*

Maternal Smoking Status	Onset of Asthma in First Year of Life	P Value
No maternal smoking	1.0	
Maternal smoking <½ pack/d	.85	.39
Maternal smoking ≥½ pack/d	2.6	.0006

* Control variables include sex, race, presence of both parents, family size, number of rooms in household, and maternal education.

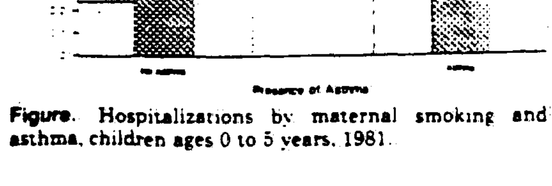

Figure. Hospitalizations by maternal smoking and asthma, children ages 0 to 5 years, 1981.

about maternal smoking were only asked in families with children aged 0 to 5 years; therefore, it is not possible to generalize these results to older children or to investigate whether more prolonged childhood exposure is associated with still higher rates of asthma or increased asthma-associated morbidity. Also, no information is available concerning maternal respiratory symptoms. In previous studies,[16,41] an increased incidence of respiratory symptoms was shown among adult smokers, and other studies have indicated that parent reports of their children's respiratory symptoms are influenced by their own respiratory symptoms. Physical examinations would not necessarily have resulted in more accurate reporting of children with asthma, because signs and symptoms of asthma are often intermittent and many children with asthma have normal baseline respiratory status between attacks. Similarly, information from medical records is notoriously incomplete.

The lack of a relationship between passive exposure to maternal cigarette smoke and hospitalizations among children with asthma in this study is puzzling. Although in occasional studies[42] there is failure to demonstrate increased bronchial reactivity among children with asthma exposed to passive smoke, in the majority of laboratory studies to date increased bronchial reactivity seems to be a fairly consistent response to passive smoking by asthmatics. The studies provide a physiologic basis for the belief that passive smoking exacerbates childhood asthma. There is surprisingly little clinical or population-based data, however, to support this belief. According to O'Connel and Long,[43] parents reported that their smoking aggravated their children's asthma and that the children's asthma improved when they stopped smoking. Murray and Morrison[11] reported 47% more symptoms among children with asthma whose mothers smoked. Tsimoyianis et al[24] found increased cough reported among 12- to 17-year-old nonsmoking athletes who had parents who smoked cigarettes. None of these studies, however, specify number of bed days or hospitalizations. Fergusson and Horwood[12] and Dodge[27] found no association between passive smoking and exacerbations of childrens' asthma. Evans et al[44] reported a 63% increase in emergency room use by children with asthma associated with smoking by one or more family member; however, they failed to demonstrate an association between passive smoking and days with asthma symptoms, hospitalization rates, or pulmonary function. The findings from the National Health Interview Survey also do not demonstrate an association between maternal smoking and increased hospitalizations among children with asthma. This finding must be viewed with particular caution, however, because with only 117 children with asthma in the sample, its statistical power is low. For example, to detect a difference in hospitalization rates of 10% (with 80% power and an α of .05), a sample three times larger than the present one is required.

The mechanism by which maternal smoking is associated with an increased prevalence of childhood asthma is currently not known. In most studies to date children's respiratory symptoms, asthma, and lung growth were correlated with postnatal passive smoking, but in several recent studies it was suggested that antenatal exposure to tobacco smoke might have separate, independent effects on pulmonary development and function. Collins et al[14] provided rat model data that suggest that maternal cigarette smoking during pregnancy is characterized by fetal lung hypoplasia with decreased lung volume and decreased numbers of alveoli. In another study[15] it was demonstrated that maternal smoking during pregnancy is associated with elevated cord blood IgE among newborns of nonallergic parents and a fourfold increased risk of the development of atopic disease (asthma, eczema, urticaria, or food allergy) before 18 months of age, suggesting that maternal smoking during pregnancy predisposes even low-risk infants to subsequent sensitization, probably in synergy with a subsequently acquired mucosal damage that would facilitate penetration of foreign matter. The estimate of children's exposure to cigarette smoke in the current study is crude, based on parent reporting of smoking during pregnancy. It seems reasonable to assume that for most mothers smoking habits remain relatively stable from pregnancy through early childhood and there is at least one study[35] to support this contention. Our data are certainly consistent with earlier findings indicating prenatal and postnatal effects on pulmonary structure and function, but it was not possible to differentiate prenatal from postnatal maternal smoking effects on the prevalence of childhood asthma.

IMPLICATIONS

In three landmark reports by the Surgeon General[2,3] and the National Academy of Sciences[4] and the recent article by Fielding and Phenow[5] similar conclusions were presented about the adverse effects of passive smoking. Although passive smoking appears to present smaller risks than active smoking, the number of people injured by passive smoking is much larger than the number injured by other environmental agents that are already widely regulated. The American Academy of Pediatrics Committee on Environmental Hazards[45]

has stated that passive smoking may be the most important source of environmental contamination and some believe that it is the most important environmental factor involved in the etiology of early asthma.[46] It is extremely unlikely that we will ever be willing or able to regulate the smoking of adults in their own homes; therefore, we must employ strategies other than coercion to help parents decrease their smoking, both for their own health as well as for their childrens' well-being.

The findings of this study should encourage renewed efforts to discourage smoking in families, especially during pregnancy and the first 5 years of children's lives. It is suggested that pediatricians may actually be able to help prevent childhood asthma if they can help parents stop smoking. Strategies that may be useful include explaining the environmental hazards of smoking to children, especially the association between maternal cigarette smoking and the increased risk of a child having asthma; encouraging parents not to smoke; and referring parents who smoke to smoking cessation programs. Low-cost smoking cessation programs for pregnant women have been shown to be effective,[47-49] but such programs have not been widely implemented or used. Two barriers to their use are the fact that insurance carriers and Medicaid generally do not pay for these programs, and physicians do not tend to refer patients to them.

The Committee on Environmental Hazards of the American Academy of Pediatrics[45] suggests that physicians routinely inquire about parental smoking habits when caring for children with chronic or recurrent respiratory symptoms. The data reported in this paper, when viewed in the context of other recent studies, suggest that this advice is not broad enough. Parents should be encouraged not to smoke, irrespective of their child's current respiratory status, or their smoking may result in the development of asthma in their children.

ACKNOWLEDGMENTS

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FANNY FARMER DIDN'T COOK UP THIS HASH

Hashing - basically an excuse to run on a surprise-filled trail and finish with beer, food and song - has reached the U.S. after years overseas, mostly in the Far East. Based on the 18th-century English school-boy game called hares and hounds, hashing was dreamed up in the 1930's by two Englishmen and an Australian living in what is now Malaysia. The trio sought to shed some pounds and shrug off a few hangovers by running around a Kuala Lumpur park.

But mere running was little dull. So the trio decided to take turns laying trails - littered with false leads - through jungles and rice fields. After navigating the course, they rewarded themselves, rather to the detriment of their original purpose, with beer in their quarters next to a club nicknamed the Hash House. (As some hashers tell it, the club barred the sweaty runners because they didn't meet its dress code.) And the hash was born.

In the ensuing decades, hashing spread among international bankers, military personnel, diplomats and others who tended to find themselves in places like Brunei with nothing to do. Now there are 80 000 hashers in more than 700 clubs in 126 countries on every continent except Antarctica.

Stout H. Following the flour is a popular sport for folks on the run. *The Wall Street Journal* October 11, 1989.

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Rubin, B.K. "Exposure of Children with Cystic Fibrosis to Environmental Tobacco Smoke" <u>The New England Journal of Medicine</u> 323(12):782-788, 1990.

ABSTRACT: Background - In children, passive exposure to environmental tobacco smoke has been associated with growth suppression and an increased frequency of respiratory tract infections. On the assumption that this association would be more pronounced in children with chronic pulmonary disease, we examined the growth, nutritional status, lung function, and clinical condition of children with cystic fibrosis in relation to their exposure to environmental tobacco smoke. Methods - We studied 43 children (age, 6 to 11 years) on entry to a summer camp and then again after two weeks in this smoke-free environment. Twenty-four of the children (56 percent) came from homes with smokers. Results - There appeared to be a dose-dependent relation between the estimate of smoke exposure (cigarettes smoked per day in the home) and overall severity of disease, as assessed by the age-adjusted rate of hospital admissions ($r = 0.58$), peak expiratory flow rate ($r = -0.39$), and measures of growth and nutrition, including weight percentile ($r = -0.37$), height percentile ($r = -0.44$), midarm circumference ($r = -0.42$), and triceps skin-fold thickness ($r = -0.31$). These effects were most evident in the girls. When only the 24 children from homes with smokers were analyzed, however, the dose-dependent relation was present only for the number of hospital admissions and for height. Among the children with good lung function ($n = 21$) or with normal weight for height ($n = 27$) at the start of camp, those who had been exposed to tobacco smoke gained significantly more weight during the two weeks of camp than did the children from smoke-free homes. Conclusions - These data suggest that passive exposure to tobacco smoke adversely affects the growth and health of children with cystic fibrosis, although the possibility cannot be ruled out that social, economic, or other factors determined both the smoking status of the household and the nutritional status of the children.

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EXPOSURE OF CHILDREN WITH CYSTIC FIBROSIS TO ENVIRONMENTAL TOBACCO SMOKE

Bruce K. Rubin, M.D., F.R.C.P.(C.)

Abstract *Background.* In children, passive exposure to environmental tobacco smoke has been associated with growth suppression and an increased frequency of respiratory tract infections. On the assumption that this association would be more pronounced in children with chronic pulmonary disease, we examined the growth, nutritional status, lung function, and clinical condition of children with cystic fibrosis in relation to their exposure to environmental tobacco smoke.

Methods. We studied 43 children (age, 6 to 11 years) on entry to a summer camp and then again after two weeks in this smoke-free environment. Twenty-four of the children (56 percent) came from homes with smokers.

Results. There appeared to be a dose-dependent relation between the estimate of smoke exposure (cigarettes smoked per day in the home) and overall severity of disease, as assessed by the age-adjusted rate of hospital admissions ($r = 0.58$), peak expiratory flow rate ($r = -0.39$), and measures of growth and nutrition, including weight percentile ($r = -0.37$), height percentile ($r = -0.34$), midarm circumference ($r = -0.42$), and triceps skin-fold thickness ($r = -0.3$[illegible]). These effects were most evident in the girls. When only the 24 children from homes with smokers were analyzed, however, the dose-dependent relation was present only for the number of hospital admissions and for height. Among the children with good lung function ($n = 21$) or with normal weight for height ($n = 27$) at the start of camp, those who had been exposed to tobacco smoke gained significantly more weight during the two weeks of camp than did the children from smoke-free homes.

Conclusions. These data suggest that passive exposure to tobacco smoke adversely affects the growth and health of children with cystic fibrosis, although the possibility cannot be ruled out that social, economic, or other factors determined both the smoking status of the household and the nutritional status of the children. (N Engl J Med 1990; 323:782-8.)

EXPOSURE to environmental tobacco smoke has been postulated to have an adverse effect on lung function[1-4] and growth[5-11] in normal children. There is a dose-dependent relation in the frequency of respiratory tract infections in infants and young children exposed to tobacco smoke.[1-3] Some studies have shown a statistically significant decline in pulmonary function in healthy children exposed to tobacco smoke,[12] and there is a suggestion that children with asthma have more frequent attacks and more severe disease when exposed to environmental tobacco smoke.[3] There is also a body of evidence relating growth retardation and weight reduction to active smoking in adults[13,14] as well as to passive smoking in children[7-11]; a similar relation has been found in infants born to mothers who smoke[5-7] and in infants born to mothers passively exposed to tobacco smoke.[15]

Cystic fibrosis is an autosomal recessive disease whose major manifestations are recurrent and chronic pulmonary infections and pancreatic malabsorption

From the University of Alberta Hospitals, Department of Pediatrics (Pulmonary), Edmonton, AB T6G 2R7, Canada, where reprint requests should be addressed to Dr. Rubin.

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with growth retardation.[16,17] Children with this disease may therefore be at increased risk for harm from exposure to tobacco smoke. We studied the relation between exposure to smoke and clinical status, growth and nutrition, and pulmonary function in a group of children between the ages of 6 and 11 years attending a summer camp for children with cystic fibrosis. The camp setting was ideal for collecting information about the children's medical history and exposure to tobacco smoke. Furthermore, this setting facilitated the organized collection of data on growth, nutrition, and pulmonary function on entry into camp and the assessment of changes in these measurements after two weeks of a balanced, high-quality diet, carefully administered medications, and physiotherapy in an environment free of tobacco smoke.

Methods

At the start of the two-week summer camp for patients with cystic fibrosis (Camp Merrywood in eastern Ontario), a medical history was obtained for each camper as part of the registration process, and all had a physical examination, which included the measurement of height, weight, and routine vital signs. After informed consent was obtained from the parents or guardians of the campers, a group of physicians, nurses, and medical students from Queen's University (Kingston, Ont.) and the University of Ottawa cystic fibrosis centers collected additional data on 43 of the 46 campers as detailed below. Incomplete data were collected for one boy who left early (for family reasons) and another who arrived a day late. One of the campers declined participation in the study. This study was approved by the March of Dimes, which coordinates Camp Merrywood, by the administrators of the camp, and by the Queen's University Human Research Committee.

The medical history was supplemented by a questionnaire that was completed by the parents. Data were collected about the severity of the camper's illness (e.g., frequency of cough, amount of sputum, and number of hospital admissions) and about his or her home, including a listing of all household members, their ages, health status (including recent respiratory tract infections), and tobacco consumption, expressed as the number of cigarettes smoked per day in the home. These data were checked for accuracy by reviewing the questionnaire both with the parent who completed the form and with the child. Historical data were further verified by cooperating Ontario cystic fibrosis centers after camp was completed.

In each participating child, midarm circumference and triceps skin-fold thickness were measured (skin-fold spring-loaded caliper, John Bull British Indicators),[18] and pulmonary function was evaluated (Vanguard spirometer and recorder, Life Support and Equipment). Clinical progress was assessed with the Shwachman–Kulczycki system,[16] which uses historical data and physical-examination results to calculate a score for the general, nutritional, and physical health of patients with cystic fibrosis. All the children were familiar with pulmonary-function testing procedures. Spirometry was repeated until three acceptable curves were produced for each child,[19] from which forced vital capacity (FVC), forced expiratory volume in one second, peak expiratory flow rate (PEFR), and expiratory flow rate measured between 25 percent and 75 percent of the forced vital capacity were recorded from the curve in which the total of FVC and forced expiratory volume in one second was largest. Pulmonary-function data were analyzed after camp by computer and expressed both in terms of absolute volumes and flow rates and as the percentages of the predicted values for Ontario children of the same height and sex.[19] The physical examination, spirometry, and anthropomorphic measurements were repeated on the last day of camp. The investigators who conducted the physical examinations, evaluated pulmonary function, and collected nutritional data were unaware of the details of the medical history — specifically, the children's exposure to tobacco smoke.

Statistical analysis was performed with the StatView 512+ statistics package (Abacus Concepts) and a Macintosh II computer (Apple Computer) and reviewed by a statistician. Comparisons between children who were exposed to environmental tobacco smoke and those who were not were made with an unpaired t-test. Changes in pulmonary function and nutritional status in the two groups of children while they were at camp were analyzed with an unweighted, two-tailed, paired t-test. Analysis of variance was used to investigate the interaction between exposure to environmental tobacco smoke and growth. Results are presented as means ±SD. All P values of less than 0.05 were considered to indicate significance.

One severely ill child required constant nasal administration of oxygen and was unable to participate in camp activities. Because this girl spent most of the camp session in the infirmary, initial data related to her growth and health were recorded, but she was excluded from analyses dealing with changes noted after camp.

Results

Patient Population and Severity of Illness

The children were 72 to 143 months of age (mean, 108.9±16.7) and had been seen at one or more of the seven cystic fibrosis centers in Ontario. There were 18 girls and 25 boys in the group that completed the study. Twenty-four of the children (56 percent) came from households with smokers (24.4±14 cigarettes smoked in the home per day), and nearly 40 percent had mothers who smoked (18.6±9.2 cigarettes per day). None of the children actively smoked.

Clinical scores indicated that as a group these children were in fairly good health. Of a possible total of 25 points, the Shwachman–Kulczycki general score for the group was 23.2±3.1, the physical score was 22.0±4.3, and the nutrition score was 22.1±4.0. There was a correlation between the total score and the number of cigarettes smoked in the home (r = −0.34, P = 0.03), but this was accounted for almost entirely by the strong correlation between the nutrition subscore and exposure to environmental tobacco smoke (r = −0.41, P = 0.006).

Because the total number of hospitalizations increases with the age of the patient, one measure of illness severity is the normalized hospital-admission rate, obtained by dividing the total number of admissions by the child's age in months. Normalization of the admission rate minimizes the effect of the broad age range of the children and more accurately reflects the severity of illness. In the group as a whole, the normalized hospital-admission rate was strongly related to the number of cigarettes smoked in the home (r = 0.58, P<0.0001) (Fig. 1). Examining data from just the 24 children exposed to tobacco smoke still yielded a significant, dose-dependent relation (r = 0.55, P<0.01). There was a significant correlation of exposure to tobacco smoke with the normalized hospital-admission rate for the girls (P = 0.0005), and analysis of variance suggested that this factor alone accounted for 57 percent of the variability. Somewhat surprisingly, the relation between exposure to tobacco smoke and the normalized hospital-admission rate was not significant for the boys.

We further compared subgroups of children according to lung function: 21 had relatively normal lung

function, as defined by an FVC of more than 80 percent of the predicted value, and 20 had impaired function (FVC <80 percent of the predicted value). (Vital capacity could not be measured in two children.) Children with poorer lung function had significantly more hospitalizations if there was smoking in the home (8.4 vs. 1.7 admissions; P = 0.05). We also compared the children with good nutritional status, as indicated by a weight for height more than 50 percent of the predicted value (n = 27), with those with poor nutritional status (weight for height <50 percent of the predicted value: n = 16), and there was a trend for more hospitalizations in malnourished children from homes with smokers (6.4 vs. 1.8 admissions for malnourished children from homes without smokers; P = 0.1).

Effect of Tobacco Smoke on Pulmonary Symptoms and Function

There was no association between exposure to tobacco smoke, expressed as the number of cigarettes smoked in the home per day, and the amount of coughing or sputum production, the number of nasal polyps, or any pulmonary-function measurement except the percentage of predicted PEFR (r = −0.39, P = 0.01). The association with PEFR was stronger in the girls (r = −0.53, P = 0.03) and was also more clearly evident in children with good lung function (95.7 percent for those exposed to tobacco smoke as compared with 118.4 percent for those not exposed; P = 0.01). There was also a weak association between the degree of digital clubbing, as measured on a four-point scale (none, mild, moderate, or severe),

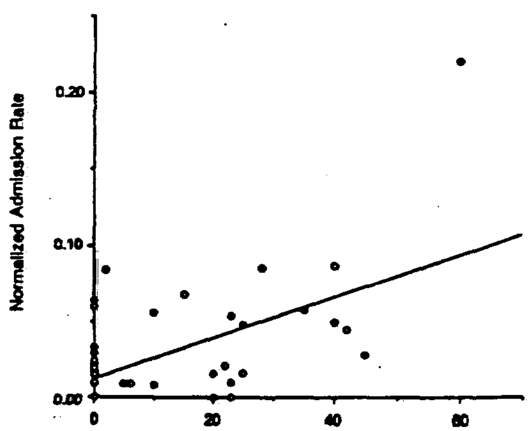

Figure 1. Normalized Admission Rate (Number of Hospital Admissions Divided by the Age of the Child in Months) as a Function of the Number of Cigarettes Smoked in the Home.

The values for the group of 43 children as a whole were r = 0.58 and P<0.0001; for the 18 girls, r = 0.76 and P = 0.0005; for the 25 boys, r = 0.15 and P = 0.50; and for the 24 children from homes with smokers, r = 0.55 and P<0.01. Girls are represented by solid circles, and boys by open circles.

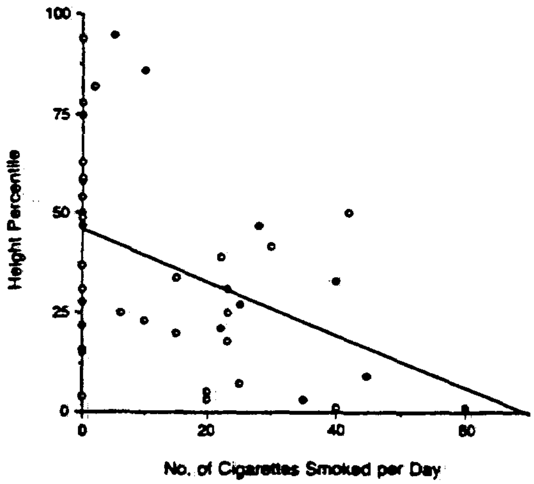

Figure 2. Children's Height Percentiles as a Function of the Number of Cigarettes Smoked in the Home.

The values for the entire group were r = −0.44 and P = 0.003; for the girls, r = −0.58 and P = 0.01; for the boys, r = −0.37 and P = 0.07; and for the group of children from homes with smokers, r = 0.52 and P<0.01. Girls are represented by solid circles, and boys by open circles.

and the number of cigarettes smoked in the home (r = 0.30, P = 0.05).

Effect of Environmental Tobacco Smoke on Growth and Nutrition

Exposure to tobacco smoke was associated most strongly with growth and nutrition (Fig. 2 through 5); a dose-dependent relation was observed for all measurements when the analysis included children not exposed to tobacco smoke (exposure level of 0). The group not exposed to tobacco smoke averaged about the 50th percentile for age for both height and weight. For the girls there was a significant relation (P<0.05) between the amount of exposure to tobacco smoke and the height percentile (25 percent of the variability) and weight percentile (33.9 percent of the variability), whereas for the boys there was a trend toward significance correlating exposure to tobacco smoke with the height percentile (P = 0.067; 13.8 percent of the variability) but no significant relation with the calculated weight percentile at the start of camp. There was a significant correlation between exposure to tobacco smoke and both the child's height (r = −0.61, P<0.0001) and the height percentile according to age and sex (Fig. 2). This relation was still valid when only the 24 children from homes with smokers were considered (r = 0.52, P<0.01). The dose-dependent relation between exposure to tobacco smoke and height was stronger for the girls (r = −0.82, P<0.0001) than for the boys (r = −0.42, P = 0.03). A similar correlation was noted between the child's weight and the number of cigarettes smoked in the home for the entire group of children (r = −0.55, P = 0.0002) and for the girls only

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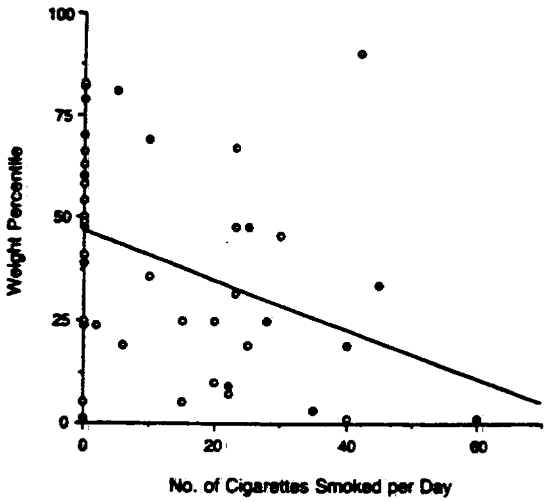

Figure 3. Children's Weight Percentiles as a Function of the Number of Cigarettes Smoked in the Home.
The values for the entire group were $r = -0.37$ and $P = 0.01$; for the girls, $r = -0.50$ and $P = 0.03$; for the boys, $r = -0.12$ and $P = 0.57$; and for the group of children from homes with smokers, $P = 0.36$. Girls are represented by solid circles, and boys by open circles.

($r = -0.77$, $P = 0.0002$), whereas there was a trend toward significance for the boys ($r = -0.33$, $P = 0.11$). There was a dose-dependent inverse correlation between the number of cigarettes smoked by family members each day and the weight percentile according to age and sex (Fig. 3), the midarm circumference (Fig. 4), and triceps skin-fold thickness (Fig. 5), but these correlations failed to achieve significance when data only for the children from homes with smokers were analyzed.

Changes after Two Weeks at Camp

During the two-week camp session significant changes were observed in measures of growth and nutritional status. These included gains in weight, weight percentile, weight-for-height percentile, triceps skin-fold thickness, and midarm circumference. Eight children lost weight over the two weeks of camp, and 29 gained weight. Those who gained weight came from homes where more cigarettes were smoked (mean number of cigarettes smoked daily, 16, as compared with 1.9 cigarettes for those who lost weight; $P<0.02$).

While at camp children from homes with smokers gained more weight than children from smoke-free homes, especially if their initial FVC was normal (Table 1) or weight-for-height percentile was more than the 50th percentile (Table 2).

Discussion

For more than 30 years, nicotine has been known to be a potent regulator of weight in both humans and animals. Tobacco smokers weigh less than nonsmokers[13,14] and gain an average of 5 kg after they stop smoking,[20] half in the first seven weeks.[21] Children exposed to tobacco smoke are smaller and lighter than their peers.[21] A strong inverse relation between children's height and the number of smokers at home was found for a sample of children in Great Britain, even when growth was adjusted for birth weight, social class, and parental height. This stunting was also unrelated to respiratory symptoms.[8] In a study of children in California, it was shown that exposure to environmental tobacco smoke had a significant ($P<0.001$) inverse and dose-dependent effect on the length at birth and the height at the age of five years that was unrelated to socioeconomic factors.[9] In Canadian children with normal birth weights, those exposed to environmental tobacco smoke were significantly shorter and lighter between the ages of 1 and 6.5 years than those who were not exposed.[11]

Children with cystic fibrosis tend to have low birth weights, and their mean height and weight during childhood are lower than those for the general population.[17,22-24] Although their nutritional requirements are increased, food intake is frequently in the range of 80 percent of the recommended daily allowance of calories and protein for age and height.[22] At all ages, female patients with cystic fibrosis have been reported to have a greater degree of growth suppression and malnutrition than male patients.[24] The mean height percentile was 38 percent for the group of girls we studied and 36 percent for the boys, but the weight-for-height percentile at the start of camp was 47 percent for the girls and 52 percent for the boys, suggesting that although these children were generally smaller than average, they were not particularly thin.

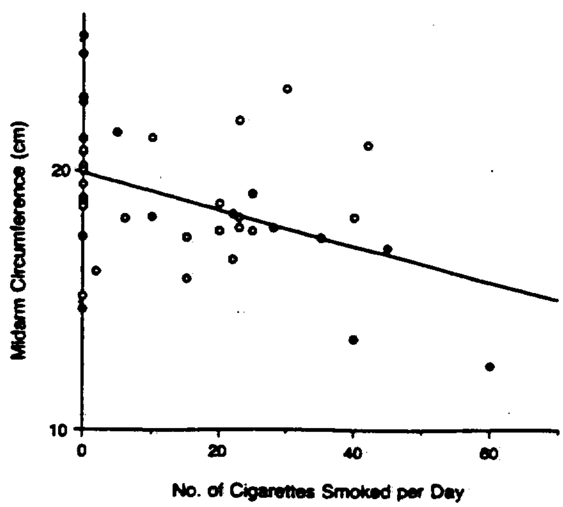

Figure 4. Midarm Circumference as a Function of the Number of Cigarettes Smoked in the Home.
The values for the entire group were $r = -0.42$ and $P = 0.006$; for the girls, $r = -0.68$ and $P = 0.002$; for the boys, $r = -0.17$ and $P = 0.42$; and for the group of children from homes with smokers, $P = 0.10$. Girls are represented by solid circles, and boys by open circles.

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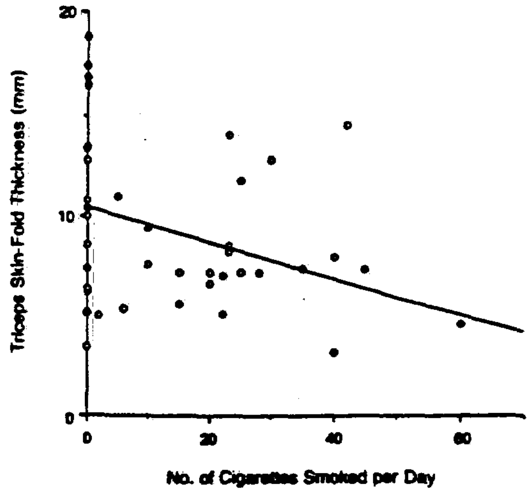

Figure 5. Triceps Skin-Fold Thickness as a Function of the Number of Cigarettes Smoked in the Home.

The values for the entire group were $r = -0.31$ and $P = 0.05$; for the girls, $r = -0.65$ and $P = 0.005$; for the boys, $r = -0.04$ and $P = 0.84$; and for the group of children from homes with smokers, $P = 0.96$. Girls are represented by solid circles, and boys by open circles.

[redacted] Even the children with normal weight-for-height percentiles were often significantly shorter than average, and this was related to the amount of exposure to environmental tobacco smoke in a dose-dependent manner.

In patients with cystic fibrosis who have malabsorption, bicarbonate secretion from the pancreas is less than 10 percent of the normal value, but patients without gastrointestinal symptoms also have a low level of bicarbonate secretion.[25] Studies of conscious dogs given intravenous nicotine equivalent to that in four cigarettes showed a dose-related inhibition of pancreatic and bicarbonate secretions.[26] Although nicotine may act by exacerbating malabsorption, we found no difference between the group with smokers in the home and those without in the degree of malabsorption, as measured by stool consistency or the number of enzyme capsules taken daily.

It has been postulated that the weight-regulating effect of nicotine is due to a lowering of the body weight's set-point.[27] The satiety center in the ventromedial hypothalamus is thought to be under positive serotoninergic control. Pharmacologic treatments that increase serotonin levels or act as agonists at the serotonin receptors decrease food intake.[28] Subacute administration of nicotine increases serotonin in the hypothalamus of rats,[29] and ventilation of cigarette smoke into isolated, perfused rat lungs decreases the rate of serotonin inactivation, which in turn increases the level of circulating serotonin.[30]

Most serotonin is stored in the platelets. Patients with cystic fibrosis tend to have higher mean platelet counts than normal children of the same age regardless of pulmonary status or antibiotic administration.[31] In a study performed 13 years ago at Camp Merrywood, Partington and Ferguson found that the average blood serotonin level in 67 children with cystic fibrosis was twice that in age-matched controls; however, no correlation was found between serotonin levels and height, weight, or skin-fold thickness.[32]

It is possible that there is a relation between lower socioeconomic status, parental smoking, and poor nutrition. Although socioeconomic status was not assessed directly in this study, children exposed to tobacco smoke did not come from larger families than those who were not exposed, nor were there more single-family homes with smokers. Furthermore, in Canada access to health care is not limited by the patient's ability to pay, and health insurance covers nutritional supplements prescribed by a physician. Other studies that have documented an effect of exposure to environmental tobacco smoke on the growth of children have failed to demonstrate a relation with socioeconomic status.[8,9]

It is also possible that exposure to environmental tobacco smoke further increases the energy expenditure of children with cystic fibrosis beyond their capacity to maintain adequate intake for growth[33]; however, the children at camp were generally much more active than they were at home, and yet there was a net gain in weight, midarm circumference, and triceps skin-fold thickness over the two-week session. [redacted] function can be maintained.

Female patients with cystic fibrosis have poorer nutrition,[24] pulmonary function,[34] and survival[24,35] than male patients at every age. There has been much speculation about the reasons for these differences. Although a much greater effect of exposure to tobacco smoke in girls might partially explain this difference, it is just as likely that both environmental tobacco smoke and some other sex-related factors could operate together to suppress the growth and influence the overall health of the female patients.

There are some limitations to the interpretation of these data. Since the children studied chose to attend camp, there could be unknown factors that made this group of children unrepresentative of the general population with cystic fibrosis, even though the summer camp is available free of charge to all children with cystic fibrosis in Ontario between the ages of 6 and 12 years.

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Table 1. Characteristics of Children with Cystic Fibrosis, According to Vital Capacity and Exposure to Environmental Tobacco Smoke.

Forced Vital Capacity*	No. of Children	Values at Start of Camp				Increase during Camp	
		Weight	Weight:Height	Skin-Fold Thickness	Midarm Circumference	Weight	Weight:Height
		kg (percentile)	percentile	mm	cm	kg (percentile)	percentile
≥80% of predicted value							
Exposed to smoke	14	25.7 (35.9)	50.9	8.4	18.7	0.85 (6.6)	9.1
Not exposed	7	32.4 (57.3)	74.3	12.8	21.1	0.013 (0.1)	0
P value		0.01 (0.06)	0.05	0.002	0.01	0.12 (0.05)	0.04
<80% of predicted value							
Exposed to smoke	9	25.3 (26.0)	41.8	7.5	17.6	0.63 (2.7)	5.2
Not exposed	11	30.0 (45.8)	49.5	10.5	19.5	0.40 (2.8)	2.9
P value		0.13 (0.12)	0.56	0.18	0.21	0.47 (0.94)	0.40

*Vital capacity could not be measured in two children.

We made no effort to collect blood or urine samples for measurement of biologic markers of exposure to environmental tobacco smoke; [redacted]. These levels correlated with the number of smokers in the home and the number of cigarettes smoked at home.[36] More importantly, we did not obtain information about past smoking by the parents or the duration of parental smoking, so it is possible that several of the children listed as coming from smoke-free homes may have had substantial exposure to environmental tobacco smoke. Studies have suggested that the number of cigarettes smoked daily in the home is more strongly related to the child's height than the number of cigarettes smoked during pregnancy or the length of the child at birth.[10]

The absence of an association of pulmonary function with exposure to environmental tobacco smoke in this study could be due to the smallness of the sample; however, the relation between such exposure and pulmonary function in healthy children is open to question[3,4] and is by no means as clear as the relation between exposure to tobacco smoke and growth.

[redacted]. We did not record the reasons for the hospitalizations, so it is possible that some were not related to cystic fibrosis. What is more interesting is that although nasal polypectomy is one of the most frequent reasons for surgery in children and adults with cystic fibrosis, there is reported to be an association between nasal polyps and good pulmonary function.[37] Although we collected data on the presence or absence of polyps at the time of the initial physical examination at camp, we did not inquire about past polypectomy surgery, nor did we find an association between the presence of nasal polyps and any measurement of nutrition or pulmonary function.

In a recent study of 173 adults with cystic fibrosis, 11 percent regularly smoked tobacco (2 to 60 pack-years), and 20 percent occasionally used marijuana.[38] Although a retrospective comparison with nonsmokers did not show faster short-term pulmonary deterioration in the tobacco smokers, there was no report of the smokers' nutritional status. The very fact that more than half the children we studied were exposed to tobacco smoke at home and that so many adults with cystic fibrosis could choose to smoke suggests that further studies are needed. It is possible that tobacco smoke decreases appetite and growth in children with cystic fibrosis to a greater degree than in the normal population. If these findings are verified by large, population-based studies, then elucidation of the mechanism of this interaction may have far-reaching implications for our understanding of growth in children with cystic fibrosis, sex differences in the clinical course, and the growth-suppressant effects of tobacco smoke in healthy persons.

Table 2. Characteristics of Children with Cystic Fibrosis, According to Weight-for-Height Percentile and Exposure to Environmental Tobacco Smoke.

Weight for Height	No. of Children	Values at Start of Camp				Increase during Camp	
		Weight	Height	Skin-Fold Thickness	Midarm Circumference	Weight	Weight:Height
		kg (percentile)	cm (percentile)	mm	cm	kg (percentile)	percentile
≥50th Percentile							
Exposed to smoke	13	26.3 (37)	125.5 (20.1)	9.3	19.2	0.70 (4.5)	5.4
Not exposed	14	32.6 (58.9)	134.6 (47.7)	13.0	21.1	0.16 (0.1)	0.6
P value		0.004 (0.01)	0.005 (0.003)	0.008	0.03	0.12 (0.03)	0.08
<50th Percentile							
Exposed to smoke	11	24.4 (23.8)	128.7 (42.4)	6.4	17.0	0.80 (5.6)	9.6
Not exposed	5	25.9 (24.2)	132.0 (33.2)	5.6	16.7	0.77 (5.3)	5.8
P value		0.64 (0.98)	0.61 (0.57)	0.49	0.87	0.95 (0.91)	0.47

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Gilljam, H., Stenlund, C., Hollsing, A.E., Strandvik, B. "Passive smoking in cystic fibrosis" <u>Respiratory Medicine</u> 84(4): 289-291, 1990.

SUMMARY: The families of 32 children with cystic fibrosis (CF) were interviewed about both their tobacco consumption and their childrens physical activities. Hospital records informed about treatment frequency, lung function and clinical score. Cystic fibrosis families smoked far more than the Swedish average and the passive smokers among our patients seemed to fare less well in all parameters. The children of smoking mothers required significantly longer periods of intravenous antibiotic treatment ($P > 0.05$). Frequent physical exercise seemed to compensate for the potential harmful effects of passive smoking and children with high physical activity living in families who smoked needed significantly less frequent antibiotic treatment than the inactive children ($P > 0.02$). Although this series is small, the results indicate that a smoke-free environment may be important for CF patients. General information is insufficient and extensive psychological support for the families is probably necessary.

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Passive smoking in cystic fibrosis

HANS GILLJAM*, CARIN STENLUND, ANNICA ERICSSON-HOLLSING AND BIRGITTA STRANDVIK

*Departments of *Lung Medicine and Pediatrics, Karolinska Institute, Huddinge University Hospital, S-141 86 Huddinge, Stockholm, Sweden*

The families of 32 children with cystic fibrosis (CF) were interviewed about both their tobacco consumption and their childrens physical activities. Hospital records informed about treatment frequency, lung function and clinical score. Cystic fibrosis families smoked far more than the Swedish average and the passive smokers among our patients seemed to fare less well in all parameters. The children of smoking mothers required significantly longer periods of intravenous antibiotic treatment ($P > 0{\cdot}05$). Frequent physical exercise seemed to compensate for the potential harmful effects of passive smoking and children with high physical activity living in families who smoked needed significantly less frequent antibiotic treatment than the inactive children ($P > 0{\cdot}02$). Although this series is small, the results indicate that a smoke-free environment may be important for CF patients. General information is insufficient and extensive psychological support to the families is probably necessary.

Introduction

The hazards of indoor environmental factors are widely recognized. In recent years, investigators have found not only an increased rate of respiratory symptoms and infections in normal children exposed to tobacco smoke (1,2) but also an effect on the children's lung function (3,4). By measuring saliva cotinine levels, parental smoking has been calculated to equal active smoking of at least 80 cigarettes a year (5). Cystic fibrosis (CF) is a chronic hereditary disease that from early infancy drastically increases the risk of serious respiratory infections. A rapid colonization by bacteria, commonly *Staphylococcus aureus* and/or *Pseudomonas aeruginosa* is observed and the airway secretion is abnormally thick and tenacious. Thus, it seems that CF children would be more at risk than others of being affected by passive smoking. Consequently, the following questions were asked: 'Do CF children daily exposed to tobacco smoke in their homes have more frequent airway infections?' 'Do they perform less well in lung function tests or do they have a poorer general state of health than CF children not exposed to tobacco smoke?'

Patients and Methods

This study was approved by the Ethics Committee at Karolinska Institutet.

Thirty-two of 64 CF patients regularly attending the departments of Pediatrics and Lung Medicine at Huddinge Hospital were excluded from the study since, for example, they no longer lived with their families or lived too far away to be interviewed. The families of 32 CF children aged 1–20 years (mean 10·5, median 12 years) were visited and interviewed by C.S. The interviews were based on a standard questionnaire. Hospital records provided data about antibiotic treatment, lung function tests and the general state of health expressed by the Shwachman score (6). A clinical score of ≥ 71 points was considered good to excellent and a score of less than 71 points mild to serious. We regarded a consumption of 1 cigarette/day or more at home as a smoking family. The patterns of colonization was similar in both groups, as was age and the use of oral antibiotics (penicillinase-stable penicillins and ampicillins). The number of days of antibiotic treatment in hospital during one year was used to measure respiratory infection. This variable was dicotomized into one group with high risk, i.e. ≥ 31 days in hospital with intravenous antibiotics, and one group with low risk, < 31 days in hospital. The lung function was assessed by FEV_1 and a rating of $\geq 70\%$ of predicted value was regarded as good while a rating of $< 70\%$ was considered poor. Physical activity was defined as regular activity on scheduled days each week. Those who were considered highly active had four or more activities during the week and the less active 0–3.

Statistical analysis was made with Chi-square with Yate's correction of Fisher's exact test.

Results

SMOKING HABITS

Twenty-two of the 32 families smoked: in five families both parents smoked; in five families it was

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Table 1 Relation between the clinical score of the CF patients and smoking in the families

Clinical score	Nonsmokers	Smokers	Total
≥71	9 (90%)	16 (73%)	25 (78%)
<71	1 (10%)	6 (27%)	7 (22%)
Total	10 (31%)	22 (69%)	32 (100%)

Table 2 Intravenous antibiotic treatment in CF patients exposed and not exposed to tobacco smoke in their homes

Days of i.v. treatment	Nonsmokers	Smokers	Total
≥31	1 (10%)	7 (32%)	8 (25%)
<31	9 (90%)	15 (68%)	24 (75%)
Total	10 (31%)	22 (69%)	32 (100%)

only the father who smoked; and, in eight families only the mother. In three families the mother and one sibling smoked and in one family only siblings. In families where smoking was confined to one room or otherwise restricted in consideration of the child, much fewer cigarettes were smoked than in families where no limits were set. The smoking habits had not changed over time.

PASSIVE SMOKING AND CLINICAL SCORE

[redacted] As shown in Table 1, six out of seven children with a clinical score <71 lived in smoking families. However, this difference was not statistically significant.

SMOKING AND AIRWAY INFECTIONS

[redacted] The most reliable records of airway infection were judged to be the number of days of *i.v.* antibiotic treatment in hospital. Seven out of eight patients requiring ≥31 days of treatment lived in smoking families and only one in a nonsmoking family. Also in the group of patients demanding less treatment, the exposed children dominated by 15 to 9. [redacted]

Table 3 Intravenous antibiotic treatment in CF patients exposed and not exposed to tobacco smoke in families with only one parent smoking

Days of i.v. treatment	Mothers		Fathers	
	Nonsmokers	Smokers	Nonsmokers	Smokers
≥31	1 (10%)	3 (38%)*	1 (10%)	1 (20%)
<31	9 (90%)	5 (62%)	9 (90%)	4 (80%)
Total	10	8	10	5

*$P<0.05$ compared to families where only the father smoked.

Table 4 Intravenous antibiotic treatment in CF patients with low and high physical activity in nonsmoking and smoking families

Days of i.v. treatment	Low activity		High activity	
	Nonsmokers	Smokers	Nonsmokers	Smokers
≥31	0 (0%)	5 (45%)*	1 (25%)	2 (18%)
<31	6 (100%)	6 (55%)	3 (75%)	9 (82%)
Total	6	11	4	11

*$P<0.02$ compared to patients with high activity living in smoking families.

Table 5 Distribution of FEV_1 values (% of predicted) in CF patients exposed and not exposed to tobacco smoke. Seven of the youngest children could not be assessed and were therefore excluded

FEV_1 (%)	Nonsmokers	Smokers	Total
≥70	5 (71%)	10 (56%)	15 (60%)
<70	2 (29%)	8 (44%)	10 (40%)
Total	7 (28%)	18 (72%)	25 (100%)

THE BENEFIT OF PHYSICAL ACTIVITY

For patients with high physical activity, passive smoking seemed to matter less (Table 4). The active children had fewer days of hospital treatment than the less active, who required significantly more treatment in hospital if the parents smoked ($P<0.02$).

PASSIVE SMOKING AND LUNG FUNCTION

The lung function of 25 patients was not correlated to passive smoking (Table 5). Seven of the smallest children had to be excluded as they could not perform a reliable spirometry.

Discussion

Persons interviewed about their tobacco habits often tend to underestimate their consumption. This is particularly true in situations burdened with guilt like the one investigated here. However, we did not want to increase the burden and therefore only one family member was interviewed and questions about smoking duration and earlier habits also had to be omitted. On the other hand, a high degree of uniformity was achieved by using only one interviewer (C.S.). Despite the small number of patients, the observed trends were evident. Similar effects have been seen in asthmatic children (7). The more pronounced effect of maternal smoking has also been observed earlier (8). [redacted] (9). The direct acute effects manifested as cough in a smoking environment hardly escapes notice. In addition the doctor had advised against smoking on several occasions. Therefore, profound psychological factors seem to govern the smoking habits. [redacted]

The suggested beneficial effect of physical activity in this study is probably due to activity itself (10), and not to a mere absence from home. It can be argued that the most severely ill patients simply were incapable of being active, but no patient in this series was disabled to that degree and there was no statistical difference in clinical status or pulmonary function between children from smoking and nonsmoking families. [redacted]

Acknowledgements

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Young, S., Le Souef, P.N., Geelhoed, G.C., Stick, S.M., Turner, K.J., Landau, L.I. "The Influence of a Family History of Asthma and Parental Smoking on Airway Responsiveness in Early Infancy" The New England Journal of Medicine 324: 1168-1173, 1991.

ABSTRACT. Background. Airway responsiveness to inhaled nonspecific bronchoconstrictive agents has been demonstrated in normal, healthy infants. However, it is unknown whether airway responsiveness is present from birth or if it develops as a result of subsequent insults to the respiratory tract. To investigate this question, we assessed airway responsiveness in 63 normal infants at a mean age of 4 1/2 weeks.

Methods. Respiratory function was measured with use of the partial forced expiratory flow-volume technique to determine the maximal flow at functional residual capacity (VmaxFRC). The infants inhaled nebulized histamine at sequentially doubled concentrations (0.125 to 8.0 g per liter), until a concentration was reached at which the VmaxFRC fell by 40 percent from the baseline value (PC40) or until a concentration of 8.0 g per liter was reached. We also assessed maternal serum levels of IgE, cord-serum levels of IgE, the infants' skin reactivity to several allergens, and the parents' responsiveness to histamine and obtained family histories of asthma and smoking.

Results. Aiway responsiveness was increased in infants with a family history of asthma (n= 19; median PC40, 0.78 g per liter; 95 percent confidence interval, 0.44 to 1.15; $P<0.01$), parental smoking (n= 13; median PC40, 0.52 g per liter; 95 percent confidence interval, 0.43 to 5.40; $P<0.05$), or both (n= 20; median PC40, 0.69 g per liter; 95 percent confidence interval, 0.37 to 2.10; $P<0.05$), as compared with the infants with no family history of asthma or smoking. The infants with no family history of asthma or smoking had a median PC40 of 2.75 g per liter (95 percent confidence interval, 1.48 to 4.00). No significant relations were detected between the immunologic variables and the PC40 in the infants.

Conclusions. This study indicates that airway responsiveness can be present early in life and suggests that a family history of asthma or parental smoking contributes to elevated levels of airway responsiveness at an early age.

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THE INFLUENCE OF A FAMILY HISTORY OF ASTHMA AND PARENTAL SMOKING ON AIRWAY RESPONSIVENESS IN EARLY INFANCY

Sally Young, B.Sc., Peter N. Le Souëf, M.D., F.R.A.C.P., Gary C. Geelhoed, M.B., B.S., F.R.A.C.P., Stephen M. Stick, M.A., M.B., B.Chir., M.R.C.P.(U.K.), Keven J. Turner, Ph.D., F.R.C.Path., and Louis I. Landau, M.D., F.R.A.C.P.

Abstract *Background.* Airway responsiveness to inhaled nonspecific bronchoconstrictive agents has been demonstrated in normal, healthy infants. However, it is unknown whether airway responsiveness is present from birth or if it develops as a result of subsequent insults to the respiratory tract. To investigate this question, we assessed airway responsiveness in 63 normal infants at a mean age of 4½ weeks.

Methods. Respiratory function was measured with use of the partial forced expiratory flow–volume technique to determine the maximal flow at functional residual capacity ($\dot{V}_{maxFRC}$). The infants inhaled nebulized histamine at sequentially doubled concentrations (0.125 to 8.0 g per liter), until a concentration was reached at which the $\dot{V}_{maxFRC}$ fell by 40 percent from the base-line value (PC_{40}) or until a concentration of 8.0 g per liter was reached. We also assessed maternal serum levels of IgE, cord-serum levels of IgE, the infants' skin reactivity to several allergens, and the parents' responsiveness to histamine and obtained family histories of asthma and smoking.

Results. Airway responsiveness was increased in infants with a family history of asthma (n = 19; median PC_{40}, 0.78 g per liter; 95 percent confidence interval, 0.44 to 1.15; P<0.01), parental smoking (n = 13; median PC_{40}, 0.52 g per liter; 95 percent confidence interval, 0.43 to 5.40; P<0.05), or both (n = 20; median PC_{40}, 0.69 g per liter; 95 percent confidence interval, 0.37 to 2.10; P<0.05), as compared with the infants with no family history of asthma or smoking. The infants with no family history of asthma or smoking had a median PC_{40} of 2.75 g per liter (95 percent confidence interval, 1.48 to 4.00). No significant relations were detected between the immunologic variables and the PC_{40} in the infants.

Conclusions. This study indicates that airway responsiveness can be present early in life and suggests that a family history of asthma or parental smoking contributes to elevated levels of airway responsiveness at an early age. (N Engl J Med 1991; 324:1168-73.)

ALTHOUGH asthma is considered to result from a complex interaction of genetic and environmental influences, there has been little recent progress in determining their relative contributions.[1] Recent developments in the measurement of respiratory function in infants[2] have allowed inhalation challenges to be used in this age group in order to obtain objective measurements of airway responsiveness (the ability of the airways to constrict in response to certain stimuli).[3] This technique is of particular interest, since airway responsiveness is the most useful objective physiologic measurement associated with the presence of asthma.[1]

The first inhalation-challenge studies in older normal infants, in which investigators used methacholine,[4] cold, dry air,[5] or histamine,[6] indicated that airway responsiveness was present in infants during the first year of life. Two questions have arisen from these studies. First, how early in infancy is airway responsiveness present? It has been speculated that persons with asthma are not born with heightened airway responsiveness but are born with a tendency to increased responsiveness after an insult to the respiratory system.[1,7] Second, is the initial level of airway responsiveness the same for all infants, or do genetic or environmental influences, or both, result in differing levels of responsiveness at birth? Specific environmental features, such as viral infections, irritants, and allergens, affect airway responsiveness in older children and adults,[1] but their influence on airway responsiveness in infants is unknown.

To investigate these two questions, we undertook a prospective, longitudinal study to determine the presence and level of airway responsiveness and its relation to a family history of asthma or parental smoking in 63 normal infants. This report presents our findings at the first assessment of the infants, at a mean age of 4½ weeks.

Methods

Subjects

Sixty-three infants, 24 girls and 39 boys, were studied at a mean age of 4½ weeks (range, 2 to 10). The criteria for inclusion were full-term gestation and an absence of perinatal problems and major congenital anomalies. At the time of the assessment, none of the infants had previously had a lower respiratory tract infection or any clinically important nonrespiratory illness. No infant had had an upper respiratory tract infection in the preceding three weeks. All infants were well at the time of the study.

The families of all the infants were recruited randomly at the prenatal clinic at Osborne Park Hospital, Perth, Western Australia. This is a peripheral metropolitan hospital with 2000 deliveries per year. The recruitment procedure began with an interview with the mother during a routine prenatal visit, at which time she was given written information on the family involvement that would be required during the proposed 12-month study period. One week after the interview, each family was contacted by telephone to determine whether they would agree to participate in the study. Signed parental consent was obtained for all infants. Over a 12-month period, 241 mothers were interviewed and 63 (26 percent) consented to participate. The study was performed with the approval of the medical ethics committees of Princess Margaret Hospital and the University of Western Australia.

Details of respiratory illness and atopy in the family and parental smoking habits were obtained with use of a modified American

From the Department of Respiratory Medicine (S.Y., P.N.L., G.C.G., S.M.S., L.I.L.) and the Clinical Immunology Research Unit (K.J.T.), Princess Margaret Hospital for Children, Perth, Australia. Address reprint requests to Miss Young at the Department of Respiratory Medicine, P.O. Box D 184, Perth 6001, W.A., Australia.

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Thoracic Society questionnaire[8] administered by a single investigator. The 63 infants were divided into four groups on the basis of their family histories of asthma and parental smoking. Those classified as having a family history of asthma were those whose parents reported asthma in primary relatives (the parents and siblings of the infant) or secondary relatives (grandparents, aunts, and uncles). Infants with a family history of smoking were those whose parents reported that either or both had smoked during the pregnancy. The four groups were defined as follows: group 1 (n = 11) — no family history of asthma in primary or secondary relatives, both parents nonsmokers; group 2 (n = 19) — family history of asthma in primary or secondary relatives (or both), both parents nonsmokers; group 3 (n = 13) — no family history of asthma in primary or secondary relatives, one or both parents smoked during the pregnancy; and group 4 (n = 20) — family history of asthma in primary or secondary relatives (or both), one or both parents smoked during the pregnancy. The responses to questions about parental smoking habits after the infant's birth indicated that all parents in groups 1 and 2 remained nonsmokers and the smoking parents in one family in group 3 and one in group 4 ceased smoking after the birth of the infant.

Assessment

Responsiveness to histamine was measured in 75 of the parents by the rapid-inhalation technique of Yan et al.[9] To assess immunologic influences on airway responsiveness, IgE was measured in maternal and cord serum[10] by the Clinical Immunology Research Unit, Princess Margaret Hospital for Children. Forty-seven pairs of samples of maternal and cord serum were analyzed.

Respiratory function was assessed by the forced expiratory flow-volume method.[7] A jacket was rapidly inflated at end inspiration, and flow was measured from the partial expiratory flow–volume curve at functional residual capacity. The jacket pressure was gradually increased over a series of forced expirations until maximal flow at functional residual capacity ($\dot{V}_{maxFRC}$) was obtained. Flow was measured with a No. 1 Fleisch pneumotachygraph (PK Morgan, Chatham, England), a Validyne DP-45 pressure transducer (Northridge, Calif.), and a Validyne CD19 amplifier. Volume values were obtained by electronic integration. The infant breathed through a molded-putty face mask attached to the pneumotachygraph. All signals were recorded on a chart recorder (Linearecorder F Wr 3801, Graphtec, Tokyo); flow and volume were monitored during the study with a Tektronix 5223 digitalizing storage oscilloscope (Beaverton, Oreg.) and recorded on tape (TEAC SR-50, TEAC Corp., Tokyo). Taped signals were transcribed to paper on a Hewlett–Packard 7090A x,y paper plotter (Waltham, Mass.). Arterial oxygen saturation was monitored throughout the study with a Nellcor N-200 E pulse oximeter (Hayward, Calif.). Supplementary oxygen was administered if arterial oxygen saturation fell below 90 percent.

Infants were studied while asleep after they were given a dose of chloral hydrate (80 mg per kilogram of body weight). The minimal jacket pressure required to produce $\dot{V}_{maxFRC}$ was established. This pressure was used in all subsequent forced expirations. Respiratory function was assessed before and after the administration of nebulized saline with an Airlife nebulizer (American Pharmaseal, Valencia, Calif.) at 6 liters per minute. This and all other nebulized agents were delivered directly to the face mask and inhaled during one minute of tidal breathing. For the base-line $\dot{V}_{maxFRC}$, we used the mean of the values for five forced expirations after the administration of nebulized saline.

The histamine challenge was carried out by administering sequentially doubling concentrations of nebulized histamine, ranging from 0.125 g per liter to a maximal concentration of 8.0 g per liter, as previously described.[6] A new concentration was delivered every five minutes, and respiratory function was assessed after each, with a minimum of five forced expirations at each measurement. The challenge was ended when a response to histamine was recorded or when the maximal concentration was reached. A response was defined as a decrease in the mean $\dot{V}_{maxFRC}$ of at least 40 percent from the base-line value. For infants who responded to histamine, the concentration that provoked a 40 percent decrease in $\dot{V}_{maxFRC}$ (PC_{40}) was derived by linear interpolation from the plot of the log histamine concentration against the percent decrease in $\dot{V}_{maxFRC}$ from base line. The coefficient of repeatability for a histamine challenge to an infant according to this protocol was 3.3 sequentially doubled concentrations.[11] We also determined the dose of histamine that provoked a 20 percent decline in the forced expiratory volume in one second in the parents (PD_{20}).

Two investigators measured airway function and determined airway response; one, who operated the equipment, was blinded to the infant's family history; the second, who recorded data on the infant's chart, had recruited the participants and completed the family-history questionnaires and was therefore aware of the family history. Because the blinded investigator identified changes in pulmonary function, no bias was introduced into the results.

Skin reactivity was assessed in all infants on the same day as, but before, the administration of chloral hydrate and the subsequent histamine challenge. The allergens used were *Dermatophagoides farinae*, perennial ryegrass pollen, cow's milk, and egg white (Hollister-Stier, Elkhart, Ind.). A positive response was defined as a wheal 2 mm or more in diameter.

Statistical Analysis

Differences in base-line values for $\dot{V}_{maxFRC}$ and PC_{40} among the groups were analyzed with use of the Mann–Whitney U test.[12] The median and confidence intervals for the median were determined with use of the Confidence Interval Analysis microcomputer program.[13,14] All values for IgE underwent logarithmic transformation before analysis. Within each family-history group, regressions were used to determine the relation between maternal serum IgE levels and cord-serum IgE levels, maternal serum IgE levels and PC_{40}, and cord-serum IgE levels and PC_{40}. Maternal serum and cord-serum IgE levels in the groups were compared with use of Student's unpaired (two-tailed) t-test.

Results

Descriptive data for the groups of infants are shown in Table 1. The infants in group 3 had a significantly lower mean birth weight than those in groups 2 and 4. All the mothers of infants in group 3 smoked during the pregnancy. Among the infants in group 4, 16 had mothers who had smoked during the pregnancy and 4 had fathers who had smoked during this time. There were no significant differences between the birth weights of infants in group 4 whose mothers had

Table 1. Characteristics of the Subjects According to Family-History Group.*

Group	Birth Weight	Weight†	Length†	Age†	Sex (F:M)
	kg	kg	cm	wk	
Group 1 (n = 11)	3.4±0.5	4.8±0.5	54.1±2.7	3.8±1.9	6:5
Group 2 (n = 19)	3.6±0.5‡	5.1±0.7	55.1±2.8	4.8±2.2	6:13
Group 3 (n = 13)	3.1±0.4	4.7±0.9	53.8±3.2	4.5±2.2	5:8
Group 4 (n = 20)	3.5±0.5§	4.8±0.7	54.3±2.7	4.6±1.9	7:13

*Plus–minus values are means ±SD. Infants in group 1 had no family history of smoking or asthma; those in group 2 had a family history of asthma but neither parent smoked; those in group 3 had no family history of asthma and at least one parent who smoked; and those in group 4 had a family history of asthma and at least one parent who smoked.

†At the time of the study.

‡$P<0.005$ for the comparison with group 3.

§$P<0.05$ for the comparison with group 3.

smoked and those of infants whose fathers (but not their mothers) had smoked or those of the infants in groups 1 and 2.

Base-line lung function for the groups is shown in Figure 1. Base-line $\dot{V}_{maxFRC}$ is expressed as a percentage of the predicted value, which was based on the predictive equation of Tepper et al.[15] The four groups did not differ significantly in base-line lung function.

Figure 2 shows the responsiveness to histamine in the four groups. Individual values for PC_{40} are given, along with the median value of PC_{40} for each group. Infants who responded to the first concentration were classified as having a PC_{40} of less than 0.125 g per liter. Those who had not responded at a concentration of 8.0 g per liter were classified as having a PC_{40} of more than 8.0 g per liter. PC_{40} values were not obtained for three infants; two were flow-limited at base line (i.e., forced expiratory flow was no greater than tidal expiratory flow) and therefore were not challenged with histamine (both in group 2), and in the case of one infant in group 4, the challenge was discontinued when upper-airway obstruction developed. Infants in group 1, who had a median PC_{40} of 2.75 g per liter (95 percent confidence interval, 1.48 to 4.00), were significantly less responsive than those in group 2 (median PC_{40}, 0.78 g per liter; 95 percent confidence interval, 0.44 to 1.15; $P<0.01$), group 3 (median PC_{40}, 0.52 g per liter; 95 percent confidence interval, 0.43 to 5.40; $P<0.05$), and group 4 (median PC_{40}, 0.69 g per liter; 95 percent confidence interval, 0.37 to 2.10; $P<0.05$). There were no significant differences among the values for PC_{40} in groups 2, 3, and 4.

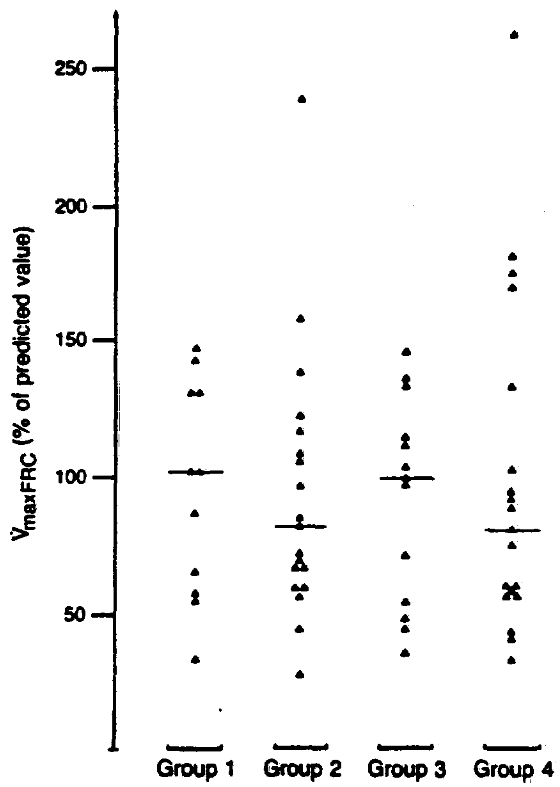

Figure 1. Individual Base-Line Values for $\dot{V}_{maxFRC}$, Expressed as a Percentage of the Predicted Value for Each Group.

The groups were defined as follows: group 1 — no family history of asthma, both parents nonsmokers; group 2 — family history of asthma, both parents nonsmokers; group 3 — no family history of asthma, one or both parents smoked; group 4 — family history of asthma, one or both parents smoked. The horizontal lines show the median percentage of predicted $\dot{V}_{maxFRC}$ for each group. Predicted values, derived with the predictive equation of Tepper et al.,[15] are based on the infants' heights; since one infant's height was not measured, only 19 data points are shown.

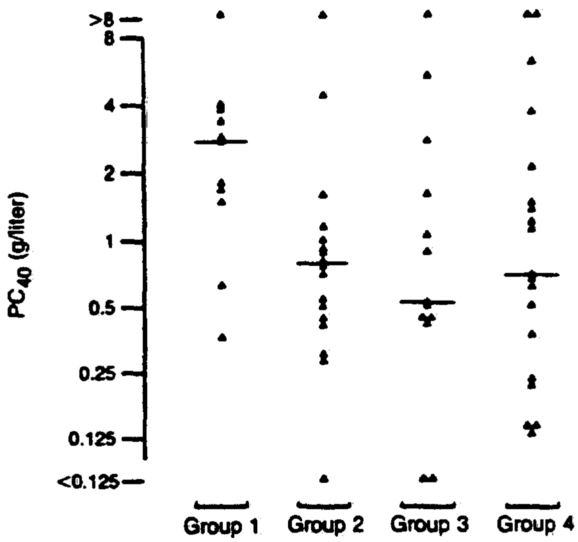

Figure 2. Individual Values for the Histamine Concentrations That Provoked a Decrease of 40 Percent in $\dot{V}_{maxFRC}$ (PC_{40}).

The groups were defined as in Figure 1. The horizontal lines show the median PC_{40} for each group. Two infants in group 2 had base-line flow limitation and therefore could not be challenged with histamine. No PC_{40} value could be determined for one infant in group 4, in whom excessive upper-airway noise developed, necessitating discontinuation of the challenge.

Of the 33 infants who had one or more parents who smoked during the pregnancy (groups 3 and 4), only 4 had fathers who smoked and nonsmoking mothers. All four were in group 4, where a family history of asthma was also present. We were therefore unable to determine the effect of paternal smoking alone.

Because there were more boys than girls in the group as a whole and because there was a particular disproportion in groups 2 and 4, comparisons of airway function were made on the basis of sex. No significant differences were found in either base-line lung function or airway responsiveness between boys and girls in the entire group of 63 infants or within the four family-history groups.

Of the 63 infants in whom skin reactivity was assessed, 7 had a positive response to one allergen and 1 had a positive response to two allergens. Responses were recorded for each of the four allergens and

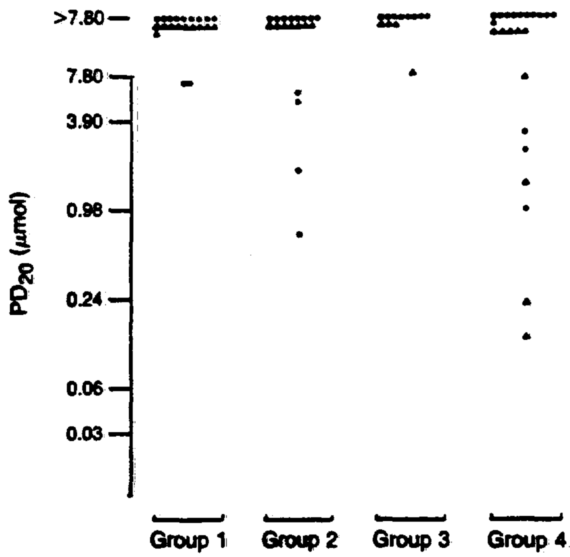

Figure 3. Doses of Histamine That Provoked a Decrease of 20 Percent in the Forced Expiratory Volume in One Second in 75 Parents of Infants in the Four Groups (PD_{20}).

The groups were defined as in Figure 1. Circles indicate mothers, and triangles fathers.

among infants in all four groups. There was no relation between the incidence of skin reactivity and the degree of responsiveness at this age.

Fourteen of the 75 parents who were tested responded to inhaled histamine. The distribution and level of response (PD_{20}) for parents of infants in each of the four groups are shown in Figure 3. There was no relation between the level of parental responsiveness to histamine and the infant's PC_{40}.

For the group as a whole, a significant positive correlation was found between the maternal serum IgE level and the cord-serum IgE level ($P<0.01$). When each family-history group was analyzed separately, however, this relation was not observed. No significant correlations were found between the maternal serum IgE level and the infant's value for PC_{40} or between the cord-serum IgE level and PC_{40}, either for the entire group of 63 infants or for the four family-history groups. There were no significant differences among the groups in either maternal venous serum IgE levels or cord-serum IgE levels (Fig. 4).

Discussion

The results of this study demonstrate that airway responsiveness to inhaled histamine is present in many normal, healthy infants soon after birth. We also found that the level of airway responsiveness in early life was increased if there was a family history of asthma, parental smoking, or both.

The development of techniques for assessing airway function in infants has made possible the study of airway responsiveness in the first two years of life, a period during which children had not been studied previously. Prendiville et al.[3] showed that infants with recurrent wheeziness were responsive to inhaled histamine. This study was followed by the work of Tepper with methacholine,[4] Geller et al. with cold, dry air,[5] and Le Souëf et al. with histamine,[6] which demonstrated that the airways of normal, healthy, asymptomatic infants were responsive to the same bronchoconstrictive agents routinely used in testing older children and adults. In these studies,[4-6] infants were studied well into the first year of life, at mean ages of 8.1 months, 5.6 months, and 7.8 months, respectively. We wished to investigate whether airway responsiveness could be detected in very early infancy. Therefore, in this study we assessed infants at a mean age of 4½ weeks, with some only 2 weeks old. A response to histamine was observed in all but 5 of the 63 infants. This finding indicates clearly that airway responsiveness is present very early in life, and it is not unreasonable to suggest that it may be present from birth.

Another reason for studying infants so early in life is that with increasing age the effect of a number of environmental insults to the airway is likely to increase. These irritants include exposure to cigarette smoke, exposure to allergens, and respiratory tract infections. These respiratory insults are known to increase airway responsiveness in older children and adults,[1] and it is possible that they also affect airway responsiveness in infants. Therefore, when airway responsiveness is assessed in middle-to-late infancy, exposure to these environmental factors makes it difficult to extrapolate the initial level of airway responsiveness. Studying infants soon after birth should help to minimize, but will not eliminate, this problem.

We found that the level of responsiveness to histamine in infants was related to the presence or absence of a family history of asthma. This finding suggests that the initial level of airway responsiveness may be genetically determined. A genetic effect on airway responsiveness in later life has been established in studies of twins[16] and of the families of persons with asth-

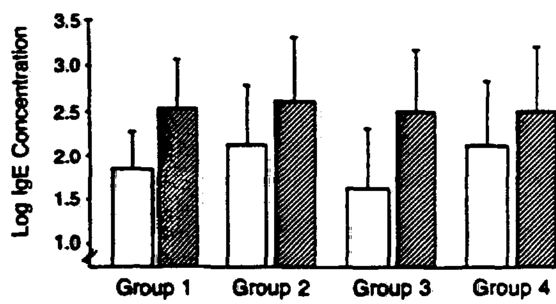

Figure 4. IgE Levels in Cord and Maternal Venous Serum, According to Family-History Group.

The groups were defined as in Figure 1. Open bars indicate mean cord-serum levels, and hatched bars mean maternal venous-serum levels. The T bars indicate the standard deviation.

ma.[17-19] Studies have shown a higher concordance for asthma and atopy in monozygotic twins than in dizygotic twins.[16] Furthermore, other studies have shown a significant relation between a history of asthma in parents and siblings and the development of asthma in early childhood.[18,19] Our study indicates that a history of asthma in primary or secondary relatives, or both, influences the level of airway responsiveness at an early age.

We also found that airway responsiveness was increased in infants whose parents reported smoking during the pregnancy. Population-based studies of airway responsiveness have found an increase in airway sensitivity among children with asthma whose mothers smoked. Martinez et al.[20] recently reported that exposure to tobacco smoke enhanced airway responsiveness in nine-year-old children; bronchial hyperresponsiveness was present in 70 percent of the children whose mothers smoked regularly during the pregnancy, but in only 29 percent of the children whose parents did not smoke during the pregnancy. Since these investigators did not find an overall association between airway responsiveness and current smoking by the mother, they suggested that fetal exposure to tobacco smoke may have had an important effect on airway responsiveness. Our study also demonstrates an association between parental smoking and the level of airway responsiveness in early infancy, although we are unable to separate the effects of prenatal and postnatal exposure to cigarette smoke. The effect of continued postnatal exposure on the base-line level of responsiveness and on the subsequent development of the symptoms of asthma is unknown. Moreover, we have not reported the amount of smoking, since it is widely recognized that the relation between the level of smoking reported by parents and the actual level of passive smoking by the fetus or infant is poor because of underreporting by parents, variations in ventilation in rooms and houses, and differences in the distance between the smoker and the infant.

Base-line lung function, expressed as a percentage of the predicted $\dot{V}_{maxFRC}$,[15] did not differ significantly among the four family-history groups, and no correlation was observed between base-line lung function and PC_{40}. These findings are in agreement with those of studies in humans[21-23] and animals[24,25] that have suggested that the caliber of the airway at base line may not be an important factor in responsiveness.

Many studies have been conducted to determine the usefulness of serum IgE levels measured at birth and during infancy in predicting the development of atopic diseases, including asthma, and skin reactivity.[26-31] These studies have indicated that a high IgE level is, in general, associated with atopy; however, all investigators have noted a wide range of IgE levels, with considerable overlap, between subjects with and without atopy. In our study, the infant's IgE level did not predict the initial level of airway responsiveness or skin reactivity, either for the group as a whole or for the four family-history groups individually. This lack of relation between atopic markers and airway responsiveness may be due to the fact that the infants were assessed before sufficient exposure to allergens had occurred. Bryant and Burns,[32] in a study of the relation between atopic status and airway responsiveness to histamine, found no correlations between serum IgE levels and the number of positive skin-prick responses or the level of airway responsiveness in a group of adults with asthma and normal adults.

Correlations have previously been found both between IgE levels in parents and those in infants[26] and between a family history of atopic diseases and the infant's IgE level.[26-31,33] We found a significant positive correlation between maternal and cord-serum IgE levels for the group as a whole, but these two measures did not discriminate among infants with different family histories. These data suggest that allergic markers are not strongly related to the initial level of airway responsiveness at this age. Because these infants are part of a longitudinal study, the potential role and relative importance of these immunologic markers may be clarified as they grow older.

In summary, we found that airway responsiveness to inhaled histamine was often present in normal, healthy, asymptomatic infants early in life. We suggest that responsiveness is present from birth and is determined both by inheritance and by exposure to parental cigarette smoking. The relation of this initial level of airway responsiveness to future levels of responsiveness, respiratory problems, and immunologic markers after exposure to environmental insults during infancy remains to be clarified.

We are indebted to the staff of the prenatal clinic and the State Health Pathology Laboratory at Osborne Park Hospital for their assistance; to Karen Krska of the Clinical Immunology Research Unit, Princess Margaret Hospital for Children, for performing the IgE assays; and to Amanda Reese, B.Sc., and Debra Turner, B.Sc.(Hons.), Department of Respiratory Medicine, for technical assistance.

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Willers, S., Svenonius, E., and Skarping, G., "Passive Smoking and Childhood Asthma," Allergy 46(5): 330-334, 1991.

The authors conducted a study to assess passive tobacco smoke exposure in children with asthma (ages 3-15 years). The authors claim that there was a statistically significantly higher excretion of cotinine in the urine of children with asthma than in the referents. The authors report a relative risk of 2.6 (95% CI: 1.2-5.3) for children with mothers who smoke. The authors conclude that "the exposure to environmental tobacco smoke in asthmatic children was higher than among healthy children, indicating that passive smoking may be a predisposing and/or aggravating factor for childhood asthma."

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Allergy, 1991, 46 (5): 330-334

Passive smoking and childhood asthma

Urinary cotinine levels in children with asthma and in referents

S. WILLERS[1], E. SVENONIUS[2] & G. SKARPING[3]

[1]Departments of Occupational and Environmental Medicine and [2]Pediatrics, Lund University, General Hospital, Malmo, and [3]Department of Occupational and Environmental Medicine, University Hospital, Lund, Sweden

Passive exposure to tobacco smoke was assessed in children with asthma (age 3-15) and in referents. There was statistically significantly ($P < 0.0005$) higher excretion of the nicotine metabolite, cotinine, in the urine of 49 children with asthma (geometric mean 10 ng/ml) compared with 77 referents (4.8 ng/ml). Maternal smoking was statistically ficantly more prevalent among the asthmatics than among the referents (relative risk: R = 2.6, 95% CI = 1.2-5.3). In conclusion, the exposure to environmental co smoke in asthmatic children was higher than among healthy children, indicating passive smoking may be a predisposing and/or aggravating factor for childhood na.

Key words: childhood asthma; cotinine; involuntary; passive smoking; predisposing factor.

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CLINICAL ASPECTS

Parental smoking cessation is of clinical importance in the asthma treatment program. Passive exposure to tobacco smoke was assessed in children with asthma and in referents. The excretion of the nicotine metabolite cotinine in urine was higher in children with asthma than in healthy children, which gives further evidence of a relationship between passive smoking and childhood asthma.

It is well known that (active) smoking is a main predisposing factor in the development of bronchial hyperreactivity and it is also known that tobacco smoke (i.e. passive smoking) irritates the bronchi in asthmatic patients (2). Tobacco smoke is probably the most important air pollution in the home, and children, especially in the Nordic countries, spend a lot of time indoors. Several studies have shown a higher frequency of respiratory infections in children of smokers (15). Further, exposure to tobacco smoke damages the airway epithelium and increases its permeability (8), which is hypothesized to be one mechanism in the development of allergy. There is some evidence of an association between passive smoking and obstructive respiratory disease in children. Thus, in a study of children at 8 and 13 years, maternal smoking was a powerful predictor of wheezing (11). Moreover, in 1986, Murray et al. (12), showed an increased severity of asthma in asthmatic children of smokers compared with those of non-smokers. However, the association between passive smoking and asthma is not consistent in the various studies.

Cotinine (the major nicotine metabolite) has been shown to be the biological marker of choice for passive smoking (9). The aim of this study was to investigate the relationship between passive smoking and asthma in children by using this objective measurement of passive exposure to tobacco smoke.

Table 1.

Cotinine levels in urine of asthmatic children and referents in relation to parental smoking habits

Parental smoking	Asthma cases Cotinine levels (ng/ml)			Referents Conine levels (ng/ml)		
	N	Geometric mean	Range	N	Geometric mean	Range
Neither	12	2.0	0.8-9.0	30	2.0	0.4-19
One parent	23	13 *	1.9-210	29	8.1	1.1-36
only father	6	8.1	4.2-20	16	5.8	1.1-26
only mother	17	15	1.9-210	13	12	2.9-36
Both	14	24 ***	5.6-56	18	9.4	1.1-44
Total	49	10 ***	0.8-210	77	4.8	0.4-44

*; *** Statistically significant differences compared with referents ($P < 0.05$; $P < 0.001$).

MATERIAL AND METHODS

Subjects

Forty-nine consecutive new cases of children with asthma (mean age 7.5 years, range 3-15) were seen during February-April 1988 at the Department of Pediatrics, Malmö General Hospital. The diagnosis of asthma was based on clinical history (i.e. recurrent episodes of cough and wheezing), and examination. At the first admittance (usually with a note of referral), a urine sample for cotinine analysis was collected. One parent was asked about both parents' smoking habits by the physician. A non-smoker was defined as a person who had never smoked or had stopped smoking more than 0.5 years ago. The number of cigarettes smoked daily (1 g of pipe tobacco was approximated to equal one cigarette) was recorded.

A referent group, from two schools, was examined during October–November 1987. All pupils and parents were asked to participate, but there was a non-response of 52%. Thus, the population sample consisted of 77 children (mean age 8.9 years, range 7–10). One parent of each child was questioned on the telephone by a nurse about both parents' smoking habits. All parents filled out a questionnaire concerning respiratory symptoms; none of the children had asthma.

The study was approved by the Ethics Committee of the Lund University.

Measurement of passive exposure to tobacco smoke

A developed capillary gas chromatographic (GC) method, using selective-ion monitoring (SIM) with deuterium labeled cotinine as internal standard, was used for the determination of cotinine in urine (17). The reproducibility of the method was good. The coefficient of variation (CV), when analysing 12 different standard samples in urine at a concentration of 5 ng/ml was 5.2%. Because there may be seasonal differences in the passive exposure to tobacco smoke (e.g. variations in room ventilation and being indoors) no urine samples were obtained during summer.

Statistics

The cotinine values were non-normally distributed. Thus, for comparison between groups (asthmatic and referents) logarithmic transformation of the cotinine values was performed. Comparisons between groups were made with t-test and Mann-Whitney U-test. Kruskal-Wallis 1-way ANOVA test was used for comparisons within groups. Kendall's tau C was used to calculate the association between parental smoking habits and cotinine levels in urine.

RESULTS

Asthmatics versus referents

In the asthmatic children, the prevalence of smoking among parents (mother and/or father) was not statistically significantly higher than among the referents (76 % and 61 %, respectively; relative risk = rr = 1.97; 95 % confidence interval 0.90–4.35; Table 1). However, maternal smoking was more prevalent among asthmatics (63 % and 40 %, respectively; rr = 2.56; 95 % CI = 1.23–5.32; etiologic fraction (EF) = 0.38).

The intensity of smoking (= number of cigarettes smoked by the parents/day) was on average, 14.2 (father 5.7; mother 8.5) for the asthmatics and 10.6 (father 5.3; mother 5.3) for the referents. This difference was statistically significant for maternal smoking (Mann-Whitney U-test; $P < 0.03$), but not among fathers, nor both parents. No significant differences in the intensity of smoking were seen if only smokers were taken into account.

There was a statistically highly significant difference between the cotinine levels in children of smokers compared with children of non-smokers, for both asthmatics and referents (geometric means: asthmatics: 2.0 and 16.4; referents: 2.0 and 8.6, $P < 0.00001$; Kruskal-Wallis 1-way Anova; Table 1). There were highly significant associations between the number of smokers and cotinine levels [Kendall's tau C = +0.70 for the asthmatics ($P < 0.00001$), and +0.55 for the referents ($P < 0.00001$)]. If, only one parent smoked, the mother's smoking habits had greater influence on the cotinine level than the father's for both asthmatics and referents; however, these differences were statistically significant only for the referents ($P < 0.01$; $t = 3.6$ and $P = 0.1$; $t = 1.7$ respectively).

The cotinine levels in the urine of asthmatic children were significantly higher than in those of the referents (Table 1, $P < 0.0005$). Further, the difference was present in all parental groups, except the non-smoker group; it was statistically significant among the "one parent" group ($P < 0.05$) and the "both parent" group ($P < 0.001$).

There were 19 asthma cases and 10 referents with cotinine values ≥ 20 ng/ml (without the range for the "neither-parent" exposed group: rr = 4.2; CI = 1.8–9.9).

DISCUSSION

In the present study, exposure to environmental tobacco smoke in asthmatic children was higher than among healthy children, as indicated by the prevalence and intensity of smoking in mothers, and the cotinine levels in urine in the children. [redacted]

This is in accordance with earlier studies. Thus, Cogswell et al. (3), showed a significantly higher prevalence of wheezing in 5-year-old children of smokers, compared with children of non-smokers, in a prospective study of children of atopic parents. Results by other investigators (12) indicated, that asthma symptom scores were higher in asthmatic children of smokers than among asthmatic children of non-smokers. McConnochie et al. (11) in a cohort study showed that maternal smoking was a strong predictor of wheezing at age 13. In accordance with this it is interesting to note that in the present study, maternal smoking was significantly more prevalent among asthmatics than among referents. The highest cotinine values (concentrations ≥ 30 ng/ml) were found among children of mothers who smoked (18 asthma and 4 referents); however, of these, seven also had a father who smoked.

One possible mechanism causing asthma may be that passive smoking predisposes to respiratory infections (4, 15), which, in turn, damages the respiratory epithelium. Also, the repair of the inflammatory changes caused by infections, may not be complete because of the continuous exposure to tobacco smoke. Thus, in a prospective study of atopic babies, the wheezing tendency decreased in children of non-smoking parents, compared with children of smokers (5). Accordingly, passive smoking appears to aggravate the state of bronchial hyper[illegible]

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other possible effect of passive smoking is to increase the permeability in the airways, which may increase the possibility for allergens to reach immunoreactive cells (8, 10, 20). Also, an allergy to some of the components in tobacco smoke has been proposed (1).

The non-response rate was high among the eligible referents. Thus, it is possible that relatively more smokers avoided joining the study. However, this is unlikely as in Sweden at the time of the study, the prevalence of smoking was 27% among both men and women (13), which is lower than in the present referents (44% and 40%, respectively). Also, as there are regional differences in smoking (18), there could be a systematic difference between the areas from where the asthmatics and referents were recruited.

The cotinine levels in our referents are in accordance with other studies of healthy children. Thus, in a study by Greenberg et al. (6) of infants under 1 year, the median value in "exposed infants" was 7.2 ng/ml. Greenberg et al. (7), also studied infants with a mean age of 18 days; the median level in children, "who excreted cotinine" was 9 ng/ml. Rylander et al. (16) found a median of 9.7 ng/ml in "4-year old children with smoking parents" and a median of 3.8 ng/ml in "non-exposed" children. The levels in some of the present asthmatic children were even higher than in adults exposed experimentally to environmental tobacco smoke (approx. 35 ng/ml (17)).

The higher cotinine levels in asthmatic children may be because passive smoking is a risk. However, an alternative explanation could be that children with asthma have a higher uptake of nicotine from the lung. Thus, we have earlier seen higher lead levels in blood in children of smokers than in those of non-smokers (19), probably due to a small airways dysfunction. However, in the present study, the cotinine levels in healthy and asthmatic children of non-smokers did not differ, which indicates that asthma is not the cause of increased cotinine excretion.

Cotinine is particularly useful in the study of children, as cotinine has a long biological half-life in children (37–160 h (14)). Cotinine levels should be valuable markers in future epidemiological studies of passive (or active) smoking as a risk factor.

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Address:
Dr. S. Willers
Department of Occupational and Environmental Medicine
Lund University
General Hospital, S-214 01 Malmö
Sweden

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Bener, A., Facharzt, A.R.A., and Al-Jawadi, T.Q., "Parental Smoking and the Risk of Childhood Asthma," Journal of Asthma 28(4): 281-286, 1991.

The authors performed a cross-sectional study of 3300 school children aged 7-12 years. Reportedly, a survey of smoking habits and attitudes conducted in Saudi Arabia "showed a positive correlation between parental smoking and asthma." The authors conclude that "this study showed a significant link between parental smoking and chest wheeze or whistling, cough, and family history of rhinitis." They also claim that "the present study results are clear evidence of a definite association between smoking in the home and bronchial asthma in young children."

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Parental Smoking and the Risk of Childhood Asthma

A. Bener, Ph.D.,* A. R. Al-Frayh Facharzt,† and
T. Q. Al-Jawadi, M.D.‡

*Department of Community Medicine
Faculty of Medicine
Kuwait University
P.O. Box 24923
Safat 13110, Kuwait
†Department of Pediatrics
College of Medicine
King Saud University
P.O. Box 2925
Riyadh 11461, ~~Saudi Arabia~~
‡Department of Pediatrics
College of Medicine
King Abdulaziz University Hospital
P. O. Box 9025
Jeddah 21413, Saudi Arabia

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ABSTRACT

In order to explore the correlation between parents' smoking habits and bronchial asthma in children, we undertook a cross-sectional study of 3300 (54% males, 46% females) school children aged 7-12 years old. A survey of smoking habits and attitudes conducted in Saudi Arabia showed a positive correlation between parental smoking and asthma. ~~This study showed a significant link between parental smoking and chest wheeze or whistling cough, and family history of rhinitis~~. Evidence is accumulating that there is a relationship between parental smoking and respiratory symptoms in Saudi children. The

Address for reprints: Professor A. R. Al-Frayh, Department of Pediatrics (39), College of Medicine, King Saud University, P.O. Box 2925, Riyadh 11461, Saudi Arabia.

present study results are clear evidence of a definite association between smoking in the home and bronchial asthma in young children, which not only may present immediate problems, but may also be a cause of illness in the future.

INTRODUCTION

The prevalence of asthma cannot be measured accurately because there is no clear definition of the condition that allows an objective measurement to be made (1); most estimates of the prevalence of asthma have been based on data from questionnaires which ask about symptoms, such as wheezing, or about asthma diagnosed by a doctor. These estimates are likely to be inaccurate because of differences in interpretation of the term "wheezing" and differences in criteria for diagnosing asthma. The prevalence of asthma cannot be measured in terms of the prevalence of lung function abnormalities since some asthmatic children have normal resting lung function (2,3).

Among the harmful effects postulated for passive smoking is a possible association between parental smoking and respiratory symptoms in children, which has been investigated in a large number of studies. Much of the research has concentrated on young children and many of the results have been positive. Increased incidence of pneumonia and bronchitis (4-8), impaired lung function (9), coughs (10), and general respiratory disorders (11,12) have been shown in young children with smoking parents. In most of these cases it is the mother's smoking habit that has received special attention because of her greater contact with the child in infancy. Although there is evidence that there is a relationship between parents' smoking habits and respiratory symptoms in children, the mechanism is not yet clear. The fact may be that the mother's smoking irritates her child's lung and facilitates the spread of infection to the lower respiratory tract (4).

The impact of parental smoking has also been detected in older children. Increased incidence of cough (13,14), wheeze (15), asthma (16,17), general respiratory diseases (18,19), and impaired lung function (20-22), are among those observed.

A questionnaire survey was conducted into the habits, attitudes, and knowledge about cigarette smoking among 12- to 18-year-old Saudi boys attending a school in Riyadh. The prevalence of smoking among Saudi schoolboys appeared to be considerably less than among their Western counterparts (23). More recently, two surveys were carried out concerning smoking habits among male students at the King Saud University in Riyadh, Saudi Arabia (24,25). These studies confirm the importance of peer group pressure and the pleasure derived from smoking as the reasons for smoking. But the importance of religion and the financial cost of smoking differs markedly from Western studies. Religious teachings have not generally been shown to be significant factors in the secular Western countries. In these studies, 48% of boys who had never smoked thought that smoking contravenes the teaching of Islam and this factor must clearly be taken into account in any health education program.

The harmful effects postulated for passive smoking is a possible association between parental smoking and respiratory conditions in children, which has been investigated in our present study. The association between parents' smoking habits and diagnosed bronchial asthma in school children in Saudi Arabia is being explored. No previous report has addressed exposure of preschool and school children to cigarette smoke in Saudi Arabia. We also showed children's cough, asthma, and wheezing bronchitis to be related to parental smoking habits, maternal and paternal smoking habits separately, and overall family smoking.

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MATERIAL AND METHODS

The children studied were the subjects of the cross-sectional population study conducted in Riyadh, Dammam, and Jeddah, cities of the Kingdom of Saudi Arabia, between January 1986 and February 1989. Those regions were chosen because of their different climates. Riyadh is located in a dry inland area. Jeddah and Dammam are located in a humid coastal region.

Riyadh, which has a dry climate, is the capital of Saudi Arabia and has a population of 2.5 million. Jeddah, which has a very humid climate, is a city of 1.5 million people on the coastal area. Dammam has a humid climate, and a population of 1 million people.

The methods used included a self-administered questionnaire to parents. Families were selected randomly. The questionnaires were completed by the parents with the help of senior medical students and under supervision of the coinvestigators and clinicians. A total of 3300 Saudi school children were recruited in the study to give details on personal data such as area of residence, social class, father's occupation, mother's occupation, age, sex, history of asthma, hay fever, eczema, family history of respiratory allergy, parental smoking habits separately and overall, family smoking and cigarette consumption at home by parents per day.

Data were analyzed on the IBM computer of the College of Medicine at the King Saud University. The statistical package program SAS was used to calculate chi-square values to assess the statistical significance of the contingency table (26). The computer package program GLIM was used to fit a generalized linear model to the data and to assess interactions between measured variables (27). The effect of parents' smoking on children's respiratory symptoms was examined by logistic regression analysis.

RESULTS

In the population study, questionnaires with a letter of explanation, were distributed to the parents of 3300 children of the Kingdom of Saudi Arabia. Parents of 3043 children (92%) gave consent for study. There was no difference in the consent rate in the three regions (Riyadh, Jeddah, and Dammam) ($p > 0.05$). The age and gender distribution were identical and the distribution of social status was not significantly different in the three regions. The age range of the children studied was 7-12 years, with a mean 9.84 years; 54% were male and 46% were female. There was no statistically significant difference in area of residence.

Table 1. Percentage of Children's Cough Related to Parental Smoking

PARENTS' SMOKING	DAMMAN %	DAMMAN NO.	JEDDAH %	JEDDAH NO.	RIYADH %	RIYADH NO.
Father only	9	(88)	15	(150)	10	(07)
Mother only	3	(27)	6	(59)	4	(43)

$p > 0.05$, not significant

Table 1 shows prevalence of children's cough related to parental smoking. As can be seen from this table, parental smoking had a significant effect on the frequency of children's cough, when maternal and paternal smoking were considered separately ($p > 0.05$). Also, Table 1 shows that there was no considerable variation in parental smoking habits in three regions.

Table 2 gives the prevalence of asthma among children who have never smoked reporting frequent asthmatic attacks related to parental smoking when compared with asthmatic children with infrequent attacks. The expected relationship between asthmatic

Table 2. Prevalence of Asthma Among Children Who Have Never Smoked Reporting Frequent Asthmatic Attacks (> 1/Month) and Infrequent Attacks (< 4/Year) Related to Parental Smoking

PARENTAL SMOKING HABIT (EITHER OR BOTH)	FREQUENT ASTHMA ATTACKS %	FREQUENT ASTHMA ATTACKS NO.	INFREQUENT ASTHMA ATTACKS %	INFREQUENT ASTHMA ATTACKS NO.
Yes	78	(268)	6	(208)
No	22	(77)	91	(2036)
Total	100	(345)	100	(2244)

$p < 0.0001$, highly significant.

Table 3. Number of Cigarettes Smoked at Home by Father

NUMBER OF CIGARETTES SMOKED	DAMMAM %	DAMMAM NO.	JEDDAH %	JEDDAH NO.	RIYADH %	RIYADH NO.
< 5 cigarettes/day	30	(277)	23	(234)	23	(248)
About 10 cigarettes/day	5	(40)	14	(140)	6	(70)
About 20 cigarettes/day	0	(0)	4	(40)	0	(0)
> 20 cigarettes/day	0	(0)	2	(14)	1	(0)
Nonsmoker	65	(601)	59	(607)	71	(770)
Total	100	918	100	1035	100	1088

$p < 0.001$, highly significant.

attacks in children and parental smoking habits appeared to be very significant. The effect of smoking on wheezing was highly significant ($p < 0.001$).

Table 3 shows the distribution of cigarettes smoked per day by fathers at home in Saudi Arabia. A statistically significant association was found between cough and the number of cigarettes smoked per day at home by fathers ($p < 0.001$).

Table 4 shows the distribution of cigarettes smoked per day by mothers at home in Saudi Arabia. A statistically significant positive association was found between cough and number of cigarettes smoked per day at home by mothers ($p < 0.001$).

The influence of smoking in the house seems to strongly influence the expression of wheeze and asthma in children. In Jeddah, 22% of asthmatic children have fathers who smoke compared with only 8.1% of nonasthmatic children. In Dammam, 16% of asthmatic children have fathers who smoke compared with only 5.14% of nonasthmatic children. Similarly, 23.36% of asthmatic children have fathers who smoke compared with only 8.79% of nonasthmatic children in Riyadh.

Table 5 shows the result of logistic regression analyses for the association between respiratory symptoms and parental smoking for all of the children. Multivariate logistic regression was estimated which predicted asthma among children from mothers smoking habits, the smoking habits of fathers, as well as whether the child had a wheezy chest or "whistling," "rhinitis," and "allergies." Significant associations were found between passive smoking and "wheezy chest or whistling" ($p < 0.0001$); "usually cough" ($p < 0.0001$); "child has family history of asthma" ($p < 0.0001$) and "child has rhinitis" ($p < 0.0001$).

Table 4. Number of Cigarettes Smoked at Home by Mother

NUMBER OF CIGARETTES SMOKED	DAMMAM %	DAMMAM no	JEDDAH %	JEDDAH no	RIYADH %	RIYADH no
< 5 cigarettes/day	11	(97)	11	(118)	20	(215)
About 10 cigarettes/day	5	(47)	8	(82)	4	(41)
About 20 cigarettes/day	0.3	(3)	2	(41)	0.2	(2)
> 20 cigarettes/day	0.1	(1)	2	(16)	0	(0)
Nonsmoker	83.6	(770)	75	(778)	75.8	(830)
Total	100	918	100	1035	100	1088

$p < 0.001$, highly significant.

Table 5. Results of Logistic Regression Analysis Showing the Association Between Respiratory Symptoms and Parental Smoking for All Children

VARIABLES	COEFFICIENT ESTIMATE	t-STATISTICS
Father smokes	0.139 ± 0.029	4.79[b]
Mother smokes	0.038 ± 0.027	1.38 NS
Chest wheezy or whistling	0.144 ± 0.023	6.72[b]
Usually cough during the day or night	0.177 ± 0.021	8.35[b]
Child has family history of asthma	0.192 ± 0.022	8.42[b]
Child has rhinitis	0.069 ± 0.027	3.07[a]

NS: Not significant.
[a] Significant at $p < 0.002$.
[b] Significant at $p < 0.0001$.

CONCLUSION

Evidence is accumulating that there is an association between parent's smoking habits and respiratory symptoms in children. This study showed a significant link between parental smoking and asthma in Saudi children. Fathers' smoking had more influence on children's asthma than mothers' smoking. It was shown that few women smoke cigarettes which is probably due to the following: (1) smoking is not common among Saudi women due to Saudi culture and (2) more likely because of the school of Islamic though forbids smoking, considering it both distasteful and unlawful.

ACKNOWLEDGMENT

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Dekker, C., Dales, R., Bartlett, S., Brunekreef, B., and Zwanenburg, H., "Childhood Asthma and the Indoor Environment," Chest 100: 922-926, 1991.

The authors studied the potential influence of indoor air quality on the respiratory health of 17,962 Canadian schoolchildren in kindergarten through second grade. Based on data from questionnaires, the authors reported that "increased reports of physician-diagnosed asthma were significantly associated with exposure to environmental tobacco smoke (OR = 1.4), living in a damp home (OR = 1.5), the use of gas for cooking (OR = 2.0) and the use of a humidifier (OR = 1.7)." The authors also reported that "wheezing without a diagnosis of asthma" was associated with ETS (OR = 1.4), home dampness (OR = 1.6) and humidifier use (OR = 1.4). Gas cooking was reportedly not associated with "wheezing without a diagnosis of asthma."

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Childhood Asthma and the Indoor Environment*

Carolien Dekker, B.Sc.; Robert Dales, M.D., F.C.C.P.; Sheryl Bartlett, Ph.D.; Bert Brunekreef, Ph.D.; and Harry Zwanenburg, M.D.

To investigate the influence of indoor air quality on respiratory health, a questionnaire-based study of 17,962 Canadian schoolchildren in kindergarten through grade 2 was carried out in 1988. The present report focuses on associations between several indoor environmental factors and childhood asthma. Increased reports of physician-diagnosed asthma were significantly associated ($p<0.001$) with exposure to environmental tobacco smoke (OR = 1.4), living in a damp home (OR = 1.5), the use of gas for cooking (OR = 2.0) and the use of a humidifier (OR = 1.7). Wheezing without a diagnosis of asthma also was associated ($p<0.01$) with environmental tobacco smoke (OR = 1.4, home dampness (OR = 1.6) and humidifier use (OR = 1.4), but not with gas cooking. Thus, several modifiable risk factors for respiratory illness may exist in Canadian homes. Further research is required to determine the nature of these cross-sectional observations. *(Chest 1991; 100:922-26)*

CI = confidence interval; OR = odds ratio

Asthma, one of the most common respiratory diseases, affects about 5 percent of the general population and 7 to 10 percent of children.[1,2] Over the past 20 years, increases in asthma morbidity and mortality have been reported in several countries.[3-7] The reasons for this are not fully understood, but increased exposure to various indoor allergens may play a role.[8]

In industrialized countries, the majority of the people spend more than 90 percent of their time indoors,[9] and thus have long duration of exposure to the potentially harmful airborne contaminants commonly found indoors. This is especially true for countries such as Canada with long cold winters. Installing additional insulation for energy conservation has reduced air exchange rates and may have increased the concentrations of indoor pollutants.[10] Exposure to contaminants from gas cooking, environmental tobacco smoke and molds in the home may increase the risk of respiratory illness.[10-12]

This report focuses on the influence of the indoor environment on asthma in a population of Canadian schoolchildren. To avoid referral bias, such as may be found in clinical studies, we also studied children with persistent wheeze but without physician-diagnosed asthma. Without the label of asthma, they would perhaps be less likely to have been counselled by a physician and less likely to have modified their home environment.

*From the Health Protection Branch, Health and Welfare Canada, Ottawa, Ontario (Ms. Dekker and Drs. Dales, Bartlett and Zwanenburg); the Department of Environmental Health, University of Wageningen, The Netherlands (Ms. Dekker and Dr Brunekreef); and the Department of Medicine and Epidemiology, University of Ottawa, Ottawa Ontario, Canada (Dr. Dales) Dr Dales is Career Scientist, Ontario Ministry of Health.

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Reprint requests: Dr. Dales, Environmental Health Center, Rm 334, Tunney's Pasture, Ottawa, Ontario, Canada K1A 0L2

Subjects and Methods

Study Population and Survey Procedures

The data used in this study were obtained from the 1988 Canadian Air Quality and Health Study, a questionnaire-based study of respiratory health and the indoor home environment.

The questionnaire was developed from the 1978 American Thoracic Society—Division of Lung Disease questionnaire, the questionnaire used in the Harvard Six Cities study, the questionnaire used in the Canadian Community Child Health study and the Environmental Inventory Questionnaire.[11,13-15] It was administered between March and April 1988 in 30 communities spanning the East to West coasts of Canada. The communities, all without significant local industrial sources of air pollution, represented six regions with differing estimated exposures to sulfate air pollution. These regions were: Southwestern and Central Ontario which had relatively high sulfate exposure, Quebec and the Maritimes which had medium exposure, and Saskatchewan and British Columbia which had low exposure. The health effects of ambient air pollution will be presented elsewhere.

Schoolchildren (n = 17,962) attending kindergarten through grade 2 received the questionnaire at school; parents or guardians answered 14,948 of the questionnaires. For the purpose of this study only the 14,059 children between 5 and 8 years of age were included. Those with cystic fibrosis (n = 17) and those who lived in mobile homes, tents, vans, trailers and boats (n = 547) were excluded.

Of the remaining 13,495 children, 10,819 children were classified into the following three study groups:

1. Children with wheezing most days or nights, or wheezing apart from colds, or attacks of shortness of breath with wheezing, but without physician-diagnosed asthma (n = 978).
2. Children with current asthma whose parents answered yes to the questions, "Has a doctor ever said this child had asthma?" and "Does he or she still have asthma?" (n = 634).
3. A comparison group of children without persistent cough, wheezing, persistent phlegm, diagnosed asthma and who had no reported chest illness, pneumonia or bronchitis within the past year (n = 9,207).

The 2,676 remaining children did not fall into any of the above categories. These children would have reported any of the following: wheezing only with colds, previous but not current asthma, persist

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Table 1—*Sociodemographic Characteristics of Children in Cohort**

Characteristics	Study Groups: Asymptomatic (n = 9,207)	Wheezing Syndrome (n = 978)	Current Asthma (n = 634)
Age (yr)			
5	19.3	21.8	18.8
6	31.7	33.0	29.0
7	33.4	30.4	38.2
8	15.6	14.8	14.0
Sex of child			
M	49.3	57.1†	62.9†
F	50.8	42.9	37.1
Race			
White	96.5	96.2	96.5
Other	3.5	3.8	3.5
Maximum parental education			
High	54.4	49.7†	53.6
Low	45.6	50.3	46.4
Sex of respondent			
M	17.8	14.1†	11.8†
F	82.2	85.9	88.2
Crowding (persons per room)			
≤0.75	70.8	72.0	76.0†
>0.75	29.2	28.0	24.0

*Values are expressed in percentages.
†Difference from asymptomatic group statistically significant at $p<0.01$.

ent cough or phlegm, recent chest illnesses, pneumonia or bronchitis.

Environmental tobacco smoke exposure was characterized by the number of household smokers. Home dampness and mold was defined as the presence of any one of the following: visible mold growth, wet or damp spots on indoor surfaces or basement water damage or leaking. Gas gooking was defined as the use of natural gas as the primary cooking fuel. Humidifier use was considered present if it was used at least three times weekly.

Covariables used to adjust the association between exposures and illness were the following: age, race, sex of child, highest level of education achieved by either parent (no post-secondary, at least some post-secondary), sex of respondent, region of residence and household crowding (persons per room).

Statistical Methods

Associations between exposures and health outcomes were assessed using chi-square tests of significance. The resulting OR with 95 percent confidence intervals were reported. To control for potential confounding factors, the OR were adjusted using multiple logistic regression and the maximum likelihood method, and the corresponding 95 percent confidence intervals were computed. The adjustor covariables were age, race, sex of child, parental education, sex of the respondent, region of residence, crowding, dampness, gas cooking and environmental tobacco smoke. The exposure variables (humidifier use, pets, heating fuels and heating systems) were each entered in the model separately. Prevalences of the environmental exposures and the covariables were reported for each of the three study groups. All statistical analyses were done using the Statistical Analysis System.[16]

RESULTS

The prevalences of asthma and the wheezing syndrome were 4.7 and 7.2 percent, respectively. Age and race distributions were similar across all three study groups (Table 1). Prevalences of childhood asthma and wheezing were higher among boys and among children whose questionnaires were completed by a female respondent. Wheezing but not asthma was more common among families with lower education, whereas asthma but not wheezing was more common in non-crowded homes.

As shown in Table 2, smoking, gas stove use, home dampness and humidifier use were more common in the homes of wheezing and asthmatic children than in the homes of asymptomatic children ($p<0.05$). The presence of furry or feathered pets appeared to be more common in the homes of wheezing children ($p<0.05$) and least common in the homes of asthmatic children. Gas and oil were more commonly used as heating fuel and forced air as a heating system in the homes of the asthmatic children than in the homes of asymptomatic children ($p<0.05$).

Table 3 shows the crude and adjusted OR with 95 percent confidence intervals for various home environmental factors. Smoking in the home was significantly associated with both wheezing and asthma ($p<0.001$). A dose-response relationship was seen; that is, the OR were larger when two or more smokers were present in the home than when there was just one smoker. Home dampness and mold and the frequent use of a humidifier also were significantly associated with both wheezing and asthma ($p<0.01$). The crude associations observed for gas stove use persisted only for asthma after adjusting for the

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Table 2—*Prevalences of Indoor Environmental Factors in the Three Study Groups**

Indoor Exposure	Study Groups		
	Asymptomatic (n = 9,207)	Wheezing Syndrome (n = 978)	Current Asthma (n = 634)
No. of household smokers:			
0 smokers	49.8	38.3	39.3
1 smoker	27.7	29.5§	30.9§
>1 smoker	22.5	32.2§	29.9§
Gas cooking			
Present	4.8	6.5†	9.4§
Absent	95.2	93.5	90.6
Dampness			
Present	34.9	47.1§	46.3§
Absent	65.1	52.9	53.7
Use of humidifier			
Present	24.8	20.7§	34.8§
Absent	75.2	70.3	65.2
Furry or feathered pets			
Present	47.3	50.4	43.1
Absent	52.7	49.6	56.9
Type of heating fuel			
Gas	30.2	32.6†	36.6§
Oil	17.2	18.3	25.2§
Wood	13.8	13.3	8.3
Electricity	37.6	34.2	28.0
Other	1.2	1.6	1.9
Type of heating system			
Forced air	38.2	37.9	46.6‡
Baseboard heater	31.6	33.3	30.5
Wood stove	26.0	23.9	18.8
Other	4.2	5.0	4.1

*Values are expressed in percentages.
†$p<0.05$ (two-sided).
‡$p<0.01$ (two-sided).
§$p<0.001$ (two-sided).

Table 3—*Odds Ratios (95% Confidence Intervals) of Indoor Factors for Childhood Asthma or Wheezing Compared with Asymptomatic Children**

	Study Groups			
	Wheezing Syndrome		Current Asthma	
	Crude OR	Adjusted OR	Crude OR	Adjusted OR
Environmental tobacco smoke				
1 vs nonsmokers	1.39	1.39 (1.17, 1.65)†	1.42	1.40 (1.13, 1.73)†
>1 vs nonsmokers	1.86	1.72 (1.44, 2.05)‡	1.69	1.58 (1.28, 1.98)‡
Dampness	1.66	1.61 (1.39, 1.85)‡	1.61	1.46 (1.22, 1.74)‡
Gas cooking	1.37	1.04 (0.77, 1.42)	2.04	1.95 (1.41, 2.66)‡
Use of humidifier	1.28	1.35 (1.15, 1.59)‡	1.62	1.66 (1.36, 2.01)‡
Furry/feathered pets	1.14	1.04 (0.90, 1.21)	0.84	0.77 (0.65, 0.93)†
Type of heating fuel				
Gas-electricity	1.19	1.09 (0.85, 1.41)	1.63	1.33 (0.95, 1.57)
Oil-electricity	1.18	0.85 (0.65, 1.12)	1.98	1.35 (0.97, 1.57)
Wood-electricity	1.06	1.03 (0.80, 1.31)	0.81	0.76 (0.52, 1.10)
Type of heating system				
Forced air-electricity	0.94	0.84 (0.69, 1.03)	1.26	1.12 (0.85, 1.42)
Wood stove-electricity	0.87	0.89 (0.73, 1.07)	0.75	0.83 (0.64, 1.07)

*See statistical methods section in text for description of methods used.
†$p<0.05$ (two-sided).
‡$p<0.01$ (two-sided).
§$p<0.001$ (two-sided).

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covariables ($p<0.001$). The association between wheezing and gas cooking was influenced by region: the crude OR was significant only for Central Ontario, 2.1 (95 percent CI 1.0, 4.2). The OR for the other regions ranged from 0.66 to 1.64 but all CI included 1. The presence of furry or feathered pets was less prevalent in the homes of children with asthma ($p<0.05$) but not with wheezing. Crude associations observed between heating fuels and symptoms did not persist following adjustment. The individual OR for each of the aforementioned indoor exposures were relatively small (less than or equal to 2.04). This means that the odds of having the symptom when exposed to any individual risk factor are generally less than twice the odds of having the symptom when not exposed. The risks, however, were higher in the 1 percent of the subjects who were exposed to more than one risk factor. In particular, the OR for the association between asthma and exposure to tobacco smoke, dampness and mold and gas stoves together was 5.4 (95 percent CI 2.7, 9.5). The maximum proportions of asthma attributable to exposures, *ie*, attributable risks, were 0.22 for tobacco smoke, 0.19 for dampness and mold and 0.02 for gas stoves.

Discussion

The present large cross-sectional study indicated that gas cooking, exposure to environmental tobacco smoke, home dampness and humidifier use were associated with the prevalence of current asthma. The latter three exposures were associated with wheezing. The OR were generally less than 2 for individual exposures, suggesting effects that were not very large. Although the OR were low, a relatively high proportion of subjects were exposed, resulting in important attributable risks: approximately 20 percent for each of tobacco smoke, and home dampness and mold. Misclassification of exposure and outcome variables (measured crudely by questionnaires) could have reduced the observed OR.

Underdiagnosis and undertreatment of childhood asthma have been reported to occur.[17,18] A diagnosis of asthma requires a visit to the physician which could be influenced by the socioeconomic status of the family. Moreover, a visit to the physician does not guarantee a correct diagnosis. First, a physician has to recognize that the child has asthma and, second, there is evidence that physicians do not want to stigmatize a child with this diagnosis.[17,18] For these reasons we also looked at children with wheezing but without physician-diagnosed asthma. Another reason for looking at this group was that families with known asthmatic children may modify their home and thereby obscure relationships between asthma and the indoor environment. Our finding that pets were less likely to be present in homes of asthmatic children supports the hypothesis that independently or upon the advice of a physician, allergenic pets have been kept out of the home.

Our results are consistent with those of others[12,19-21] in showing that home dampness is associated with both current asthma and wheezing syndromes. However, the results do not allow identification of causal mechanisms. Home dampness reflects inadequate ventilation which may cause increased concentration of various contaminants. House dust mites and fungi are both known to be more prevalent in damp homes, and they are also both known to produce substances that may trigger allergic reactions;[10] Fungi may, in addition, produce mycotoxins causing adverse health effects,[10] but there is yet very little direct evidence showing that this mechanism is responsible for the observed associations between home dampness and respiratory disease.

Independent of reported home dampness and visible mold growth, humidifier use was associated with both wheezing and asthma. Possible explanations include air contamination by microorganisms colonizing wet surfaces or particles from the water supply. Alternatively, the presence of wheezing or asthma may have prompted parents to humidify the air hoping to relieve symptoms. Fielding and Phenow,[22] in a recent review, pointed out that some studies but not others have been able to detect adverse effects of environmental tobacco smoke exposure on asthma. Our results clearly support such an association. The OR was approximately 1.5, highly statistically significant at $p\leq 0.001$, and a dose-response gradient was detected.

Gas cooking which emits nitrogen dioxide has variably been associated with increased respiratory symptoms.[11,23,24] We demonstrated statistically significant effects which persisted for current asthma but not wheezing following adjustment. This finding must be treated with caution, however, because of the few subjects with asthma in our study who were exposed ($n = 60$). It is possible that unmeasured characteristics of this particular group are in fact responsible for the observed association with gas cooking.

Apart from indoor pollutants, we found that the sex of the questionnaire respondent was related to the reporting of asthma and wheeze. Apparently, female respondents (usually the child's mother), were more aware of their children's symptoms than male responders. We therefore recommend that this potential confounder be taken into consideration when planning future studies.

Modifying the indoor environment is an important consideration in asthma management. Clinicians often emphasize dust control, removal of furry or feathered pets from the home, and more recently, avoidance of environmental tobacco smoke. We have found cross-sectional associations between several modifiable in-

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door exposures and respiratory illness. Considering the prevalence and morbidity attributed to asthma in our society, the influence of these exposures deserves further study.

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Oldigs, M., Jorres, R., and Magnussen, H., "Acute Effect of Passive Smoking on Lung Function and Airway Responsiveness in Asthmatic Children," Pediatric Pulmonology 10: 123-131, 1991.

The authors conducted an environmental exposure chamber study on 11 children with bronchial asthma of the ages 8-13 years. The authors evaluated the possible effects of a 1-hour exposure at rest (20 ppm CO). Nine of the subjects were on regular therapy; however, drugs were withheld at least 6 hours prior to each study session. After the exposure, a histamine challenge was performed on the children. There were reportedly no differences in lung function or histamine challenges between Sham exposed and ETS exposed children. The authors concluded that "the main symptoms during passive smoking were irritation of the eye and the nasopharynx" and that "in children with mild bronchial asthma 1 hour of passive cigarette smoking does not cause consistent changes of lung function and bronchial responsiveness."

Pediatric Pulmonology 10:123–131 (1991)

Acute Effect of Passive Smoking on Lung Function and Airway Responsiveness in Asthmatic Children

Maike Oldigs, MD, Rudolf Jörres, MS, and Helgo Magnussen, MD

Summary. The effect of a 1-hour exposure at rest during passive cigarette smoking (20 ppm CO) or Sham was investigated in 11 children with bronchial asthma (age range, 8–13 yr; ten boys, one girl). Nine of the subjects were on regular therapy with inhaled β_2-agonists and disodium cromoglycate. Both drugs were withheld at least 6 hours prior to each study session. Exposure was performed in an environmental chamber. Before and immediately after exposure, lung function and symptom scores were determined. After exposure, a histamine inhalation challenge was performed to determine the concentrations that caused a 100% increase in SRaw ($PC_{100}SRaw$) and a 20% fall in FEV_1 ($PC_{20}FEV_1$). Mean (SD) SRaw before and after Sham was 8.7 (3.6) and 9.0 (3.2) cmH_2O·s, and mean FEV_1 (SD) was 1.97 (0.32) and 1.98 (0.40) L, respectively. Before and after cigarette smoking, mean SRaw (SD) was 10.4 (5.3) and 9.4 (3.3) cmH_2O·s, and mean FEV_1 (SD) was 1.95 (0.37) and 1.94 (0.35 L, respectively. Geometric mean (SD) $PC_{100}SRaw$ and $PC_{20}FEV_1$ after Sham was 1.39 (3.0) and 0.70 (2.7) mg/mL, and after passive smoking 1.65 (2.5) and 0.96 (2.3) mg/mL, respectively. There were no statistical differences in lung function and PC values between Sham and passive cigarette smoking. The main symptoms during passive smoking were irritation of the eye and the nasopharynx. Our observations suggest that in children with mild bronchial asthma 1 hour of passive cigarette smoking does not cause consistent changes of lung function and bronchial responsiveness. Pediatr Pulmonol 1991; 10:123–131.

Key words: Environmental chamber exposure, pre-exposure and Sham exposure comparisons; symptom scores; specific airway resistance and FEV_1; $PC_{histamine}$; urinary cotinine concentration

INTRODUCTION

Subjects with bronchial asthma are characterized by airway hyperresponsiveness to a variety of stimuli. Cigarette smoke is considered to be a common stimulus that may affect subjects with asthma.[1–3] In children, the adverse effect of chronic passive smoking on respiratory symptoms has received increasing attention.[4–7] In some of these investigations an association between parental smoking habits and acute lower respiratory illness,[8–12] respiratory symptoms,[13–16] prevalence and severity of asthma,[13,17,18] impaired lung function, and bronchial responsiveness[10,12,13,16,17,19–23] could be demonstrated. In contrast to chronic exposure, little is known on the acute effect of passive smoking in children. We therefore studied symptoms, lung function, and airway responsiveness of children with bronchial asthma before and after 1 hour exposure to cigarette smoke as compared to control conditions.

MATERIALS AND METHODS

Patients

We investigated 11 children (10 boys, 1 girl) with allergic bronchial asthma ranging in age from 8 to 13 years [mean (SD) 10.4 (1.4) yr]. Individual patient characteristics are given in Table 1.

The diagnosis of bronchial asthma was established in all children within at least 1 year before entering the study and patients had been followed for a longer period of time in our out-patient department. The children were not selected on symptoms induced by previous exposure to cigarette smoke. Diagnosis was based on typical symptoms, reversible airflow obstruction, bronchial hyperresponsiveness to histamine, and a postitive prick skin test to at least one common allergen (Allergopharma, Reinbek, Germany). Six of 11 patients showed elevated IgE (>150 IE/mL), and 6 children had an

From the Krankenhaus Groshansdorf, Zentrum für Pneumologie und Thoraxchirurgie, LVA Freie und Hansestadt Hamburg, Germany.

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Address correspondence and reprint requests to Dr. H. Magnussen, Krankenhaus Grosshansdorf, Wöhrendamm 80, 2070 Grosshansdorf, Germany.

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TABLE 1—Data of Individual Patients

Patient	Sex	Age (yr)	Weight (kg)	Height (cm)	Atopy	IgE (IE/mL)	Eosinophils (counts/mm³)	PEF_{min} (L/min)	PEF_{max} (L/min)	VC[a] L_{BTPS}	FEV_1 (% pred.)	$PC_{20}FEV_1$[b] (mg/mL)	Therapy[c]
1	M	12	50	165	+	92	563	400	480	3.68	97	0.09	B.D
2	M	13	42	154	+	114	350	280	330	2.18	76	0.34	B.D
3	M	11	35	142	+	524	422	320	440	2.35	97	0.73	B.D
4	M	9	38	140	+	219	100	300	380	2.46	110	1.25	B.D
5	M	10	35	150	+	518	441	280	340	2.48	88	1.72	B.D
6	M	11	40	149	+	146	319	300	380	2.60	111	1.02	B.D.iC
7	M	11	41	151	+	101	181	330	400	2.60	107	1.13	B.D
8	M	9	40	141	+	269	143	240	270	1.90	85	0.12	B.D
9	M	8	26	137	+	137	147	210	330	1.82	90	1.28	—
10	M	10	36	142	+	361	422	280	350	3.00	130	0.46	B.D
11	F	10	35	143	+	185	293	150	220	2.20	98	0.30	—
Mean		10.4	38	147		242	307	281	356	2.48	99	0.54	
SD		1.4	6	8		159	149	65	73	0.52	15	2.70	

[a]VC, inspired vital capacity. For other definitions see text.
[b]Geometric mean values and geometric standard deviations of mean.
[c]Therapy: B, inhaled β_2-agonists; D, disodium cromoglycate; iC, inhaled corticosteroids.

increase of eosinophils in peripheral blood (> 300/mm³).

In all subjects the severity of asthma required a long-term therapy, which had to be continued in 9 of 11 children during the study period. All children on therapy received disodium cromoglycate, two puffs two to four times per day. Each puff of disodium cromoglycate (1 mg) was combined with 0.05 mg fenoterol (Ditec) or 0.5 mg reproterol (Aarane) as a β_2-adrenoceptor-agonist. An additional subject inhaled beclomethasone dipropionate (400 µg/day). In all children, this therapeutic regime was sufficient to control the disease and allow normal activities. This is also reflected by the minimum morning, before therapy (PEF_{min}) and maximum daytime peak expiratory flow values (PEF_{max}), which were measured regularly (Table 1). In the 9 asthmatic children receiving regular therapy, the severity of the disease allowed discontinuation of inhalation therapy at least 6 hours prior to each study session without precipitating symptoms or deteriorating lung function (subject no. 6 continued beclomethasone inhalation during the study period).

Spirometry, measured at least 6 hours after inhaling a bronchodilator, was within normal limits. In all children the provocative concentration of inhaled histamine necessary to decrease FEV_1 by 20% from baseline was less than 8 mg/mL (Table 1), thus demonstrating airway hyperresponsiveness (see Histamine Inhalation Challenge, below). During the study period and within the 2 weeks preceding the study no child suffered from an upper respiratory tract infection or experienced an uncommon burden of allergen; therefore, all included children were considered to be currently clinically stable. None of the children had ever actively smoked cigarettes; six of them were exposed to cigarette smoke at home (Table 2). Children and parents were informed about the aim of the study and gave their consent.

Cigarette Smoke Exposure

Exposure Chamber

The study was performed in a 24 m³ exposure chamber. To ensure homogeneous concentration of cigarette smoke the air was moved by fans. Sampling parts were distributed within the chamber to check for gradients of gas concentrations and particle density. Cigarette smoke was generated by a smoking machine designed in our laboratory that took one puff per cigarette per minute (according to DIN 10240). To achieve the target concentration of about 20 ppm CO, on average two cigarettes were smoked simultaneously. We used filter cigarettes of a leading brand with a nicotine content of 0.9 mg and tar content of 13 mg per cigarette.

Measurement of Exposure Conditions

The level of cigarette smoke exposure was determined by measuring CO, NO_x, particle density, nicotine, acetaldehyde, formaldehyde, acrolein, and ammonia. Concentration of CO was measured continously by an infrared gas analyzer (Unor 6N, Maihak AG, Hamburg, Germany); its calibration was checked daily by a certified span gas (Linde AG, Unterschleisshein, Germany). Concentration of NO_x was measured by a chemiluminescence nitrogen oxides analyzer (8840, Monitor Labs Inc., San Diego, CA), which was calibrated regularly by a permeation tube calibrator (model 8550, Monitor Labs Inc., San Diego, CA). Particle density was monitored continuously by measuring optical particle density (RAM-1, GCA/Environmental Instruments, Bedford, MA) using a 4 µm precollector. Optical particle density

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TABLE 2—Ratios of Urinary Cotinine to Creatinine and Reported Parental Smoking Habits

Patients no.	Cotinine/creatinine (ng/mg)	Paternal smoking	Maternal smoking
1	9.4	+	−
2	5.1	+	−
3	33.6	−	−
4	2.8	+	−
5	1.5	−	−
6	0.4	−	+
7	3.5	−	+
8	0	−	−
9	12.5	+	−
10	0	−	−
11	0	−	−

was calibrated in regular intervals gravimetrically by taking filter probes (Millipore, FALP 03700, Type FA) from total sampling volumes of 17–73 litres of air. Nicotine, acetaldehyde, formaldehyde, acrolein, and ammonia were determined using commercially available sample tubes and filters at sampling volumes ranging between 3 and 100 L of air. Analysis was performed by gas chromatography (nicotine), by high performance liquid chromatography (acetaldehyde, formaldehyde, acrolein), and by the indophenol method VDI 2461 (ammonia). Temperature and relative humidity were measured at the beginning and at the end of each exposure.

Estimation of Chronic Smoke Exposure

To estimate chronic passive smoke exposure at home we measured urinary cotinine concentration as a biological marker. Cotinine was determined in triplicate from morning urine specimens collected on the second study day. Urine cotinines were obtained in an environment free of smoking. Urine was stored at −20°C until assayed. Cotinine was measured by RIA[24] and corrected for creatinine excretion (Table 2).

Assessment of Symptoms

The chest of each subject was auscultated before and immediately after exposure. To estimate severity of symptoms induced by exposure, the children and their parents were instructed to check an ordinal scale ranging from 0 to 10 in order to determine severity of eye, nose, and throat irritation, cough, chest tightness, and headache. Zero indicated no perceptible symptom and 10 almost intolerable severity of the respective symptom.

Lung Function Measurement

Airway resistance (Raw) during breathing at 1 Hz frequency and thoracic gas volume (TGV) were measured by a volume-constant body plethysmograph (Bodytest, E. Jaeger, Würzburg, Germany) connected to a Computer (PDP 11/04, Digital Equipment Corp., Maynard, MA). Raw was multiplied by the corresponding TGV to obtain specific airway resistance (SRaw). Raw was measured during up to four breathing cycles. FEV_1 was assessed by a pneumotachograph immediately after body plethysmography. Measurements were repeated four times. For analysis, the average of four values of SRaw and the average of the two maximum values of FEV_1 were computed.

Histamine Inhalation Challenge

Bronchial challenge with histamine was performed according to the guidelines of Chai et al.[25] using a breath-synchronized pressure valve. The aerosols were generated during 0.6 s at the beginning of five slow inspirations from FRC to TLC, the nebulizer output being 80 µL of solution per five nebulizations. Saline solutions of histamine diphosphate (Sigma Chemie, Deisenhofen, Germany) were prepared daily. After a buffer solution, the subjects inhaled doubling concentrations of histamine, starting with 0.05 mg/mL histamine. Lung function was measured 1 and 3 min after inhalation. The challenge was stopped after at least a 100% increase of SRaw and a 20% fall in FEV_1. Dose-response curves were constructed by plotting SRaw and FEV_1 against log histamine concentration. By linear interpolation, the provocative concentrations of histamine (in mg/mL) were computed necessary to increase SRaw by 100% ($PC_{100}SRaw$) and to decrease FEV_1 by 20% ($PC_{20}FEV_1$) from baseline. With this method, hyperresponsiveness was assumed if PC values were below 8 mg/mL.[26]

Experimental Protocol

Each patient was studied on 3 days within a 2 week period. All investigations were performed at least 6 hours after the last inhalation therapy. On the first day recent history was taken and a physical examination performed. Lung function and airway responsiveness to inhaled histamine were measured. In case of stable clinical conditions, normal lung function, and airway hyperresponsiveness, the children and their parents were instructed about the experimental procedure. They were provided with sampling probes for collecting morning urinary specimens. Exposures to ambient air (Sham) and to cigarette smoke were performed on the second and third study days, respectively.

On exposure days, subjects rested for 10 min after entering the laboratory. After auscultation of the chest, assessment of symptoms, and measurement of baseline lung function, the children entered the exposure chamber. They were always seated at the same place inside the chamber. Five minutes before the end of exposure, symptoms were assessed again. Immediately after exposure, auscultation of the chest and lung function mea-

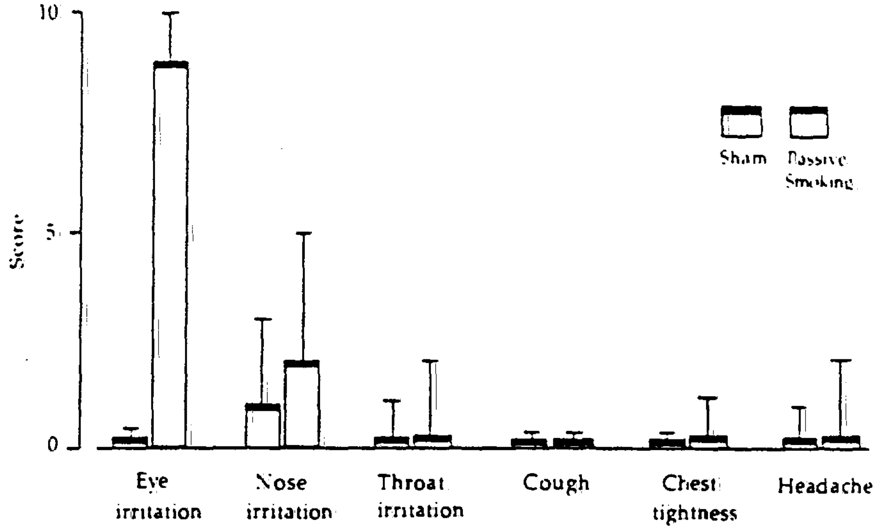

Fig. 1. Median and 90% percentile of symptom score after Sham and passive smoke exposure.

surement were performed. Histamine inhalation challenge was started 15 min after the end of exposure.

Statistical Analysis

The hypothesis of normal distribution of data was tested by normal probability plots and tests. We performed a two-way ANOVA (random factor patient) on the lung function data of the control day and before and after Sham or exposure to smoking. Lung function data before and after Sham or exposure were analyzed by pooling all patients and by a two-way ANOVA. This analysis should reveal a specific effect of exposure by testing the interaction term. We have chosen paired t-tests as a posteriori tests after applying the appropriate Bonferroni correction of the multiplicity of tests.[27] Lung function parameters before and after both exposures and control values were compared by the paired t-test. We performed paired t-tests also on the differences between before-after and during exposure to Sham or ETS, therefore adjusting for possible differences in baseline values between exposure days. PC values were analyzed as logarithms as is common in the literature, and the log PC values after both exposures and the control values were also compared by paired t-tests. Statistical significance was assumed for $P < 0.05$.

RESULTS

Exposure Conditions

During Sham and cigarette smoke exposure, mean (SD) environmental temperature was 24.1 (1.6)°C and mean relative humidity was 51 (3)%, with no difference between the study days. During passive smoke exposure, mean (SD) total particle density was 2,743 (348) $\mu g/m^3$ and nicotine content was 397 (78) $\mu g/m^3$. Mean (SD) concentrations were 20.5 (0.5) ppm for CO, 0.90 (0.09) ppm for NO_x, 0.13 (0.01) ppm for formaldehyde; 0.50 (0.05) ppm for acetaldehyde, 0.081 (0.017) ppm for acrolein, and 5.69 (3.35) ppm for ammonia. During exposure with ambient air, mean (SD) CO was 0.1 (0.3) ppm and mean (SD) total particle density was 17 (57) $\mu g/m^3$.

Symptoms During Exposure

In all children, auscultation of the chest revealed normal breath sounds before and after exposure to Sham and cigarette smoke, respectively. Eye irritation was experienced by all subjects during smoke exposure (Fig. 1). Nasal congestion was reported by 9/11 children after cigarette exposure and 5/11 after Sham. After smoke exposure, throat irritation occured in 3/11, cough in 0/11, chest tightness in 3/11, and headache in 3/11 children. Except for eye irritation, the frequency and intensity of the symptoms did not differ between cigarette smoke and Sham exposure (Fig. 1).

Variability of Baseline Lung Function

Mean (SD) SRaw before Sham and smoke exposure was 8.7 (3.6) and 10.4 (5.3) $cmH_2O \cdot s$, respectively. These values were not significantly different from each other nor from the mean (SD) SRaw value of 8.5 (2.8) $cmH_2O \cdot s$ measured upon entry into the study (control; Table 3). Mean (SD) FEV_1 before Sham and cigarette smoke was 1.97 (0.32) and 1.95 (0.39) L, respectively. These values were not significantly different from each other nor from the mean (SD) FEV_1 value of 1.95 (0.39) L when entering the study (control; Table 3). Mean (SD) values of individual coefficients of variation for the three

TABLE 3—SRaw (in $cmH_2O \cdot s$) and FEV_1 (in L) Before (Pre) and After (Post) Exposure to Ambient Air (Sham) or Passive Smoking and at the Control Day

	Control		Sham				Passive smoking			
			SRaw		FEV_1		SRaw		FEV_1	
Patient	SRaw	FEV_1	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	13.2	2.68	12.5	10.6	2.60	2.84	9.9	11.1	2.76	2.81
2	8.1	1.74	5.9	7.9	1.93	1.86	8.6	9.4	1.84	1.82
3	10.7	1.75	12.6	12.8	1.75	1.57	9.6	8.8	1.74	1.97
4	10.1	1.90	4.6	7.3	2.13	2.11	11.1	9.3	1.83	1.84
5	10.5	1.86	11.9	12.7	1.71	1.75	14.3	14.0	1.47	1.55
6	8.1	2.30	9.0	7.8	2.27	2.32	10.5	8.8	2.23	2.26
7	5.2	2.28	5.8	4.2	2.21	2.33	4.6	4.4	[illegible]	1.74
8	4.0	1.52	6.6	7.2	1.76	1.75	6.4	6.2	[illegible]	1.78
9	5.4	1.47	3.5	4.4	1.82	1.69	5.5	5.4	[illegible]	1.72
10	10.8	2.33	13.9	13.0	2.07	2.10	23.9	15.0	2.21	2.13
11	7.8	1.64	9.7	10.6	1.47	1.50	9.7	10.6	1.63	1.71
Mean	8.5	1.95	8.7	9.0	1.97	1.98	10.4	9.4	1.95	1.94
SD	2.8	0.39	3.6	3.2	0.32	0.40	5.3	3.3	0.39	0.35

repeated determinations of SRaw and FEV_1 were 21 (11) and 6 (4)%, respectively.

Lung Function Changes During Exposure

Mean (SD) SRaw before and after 1 hour exposure to ambient air (Sham) was 8.7 (3.6) and 9.0 (3.2) $cmH_2O \cdot s$ with no statistically significant difference (Table 3). Mean (SD) FEV_1 before and after Sham was 1.97 (0.32) and 1.98 (0.40) L with no significant difference. The mean (SD) change of SRaw was 0.23 (1.48) $cmH_2O \cdot s$, and the mean (SD) change of FEV_1 was 0.01 (0.11) L. In percentages the changes of SRaw and FEV_1 induced by Sham ranged from −28 to +59% and from −10 to +9%, respectively.

Mean (SD) SRaw before and after 1 hour exposure to cigarette smoke was 10.4 (5.3) and 9.4 (3.3) $cmH_2O \cdot s$. Mean (SD) FEV_1 before and after smoke exposure was 1.95 (0.39) and 1.94 (0.35) L (Table 3, Fig. 2). Values before and after exposure were not significantly different. The mean (SD) change of SRaw was −1.01 (2.79) $cmH_2O \cdot s$, and the mean (SD) change of FEV_1 was −0.01 (0.21) L. In percentages the changes of SRaw and FEV_1 during passive smoking ranged from −37 to +12% and from −25 to +13%, respectively.

Airway Responsiveness During Exposure

Geometric mean (SD) $PC_{100}SRaw$ and $PC_{20}FEV_1$ before entry (control) were 0.85 (2.4) and 0.54 (2.7) mg/mL (Table 4). Geometric mean (SD) $PC_{100}SRaw$ and $PC_{20}FEV_1$ measured after Sham were 1.39 (3.0) and 0.70 (2.7) mg/mL. Geometric mean (SD) $PC_{100}SRaw$ and $PC_{20}FEV_1$ after exposure to cigarette smoke were 1.65 (2.5) and 0.96 (2.3) mg/mL (Table 4). $PC_{100}SRaw$ and $PC_{20}FEV_1$ were not significantly different between Sham, cigarette smoke exposure and control. As determined from Sham and control, the mean (SD) values of individual variability of $PC_{100}SRaw$ and $PC_{20}FEV_1$ were 1.0 (0.5) and 0.9 (0.6) doubling concentrations of histamine.

DISCUSSION

Our observations demonstrate that in children with mild bronchial asthma 1 hour of passive smoking produced mainly eye irritation but no consistent changes of lung function and bronchial responsiveness to inhaled histamine. Acute pulmonary response to passive smoking has not been studied in asthmatic children. Previous studies on the acute effect of passive smoking were performed in adult asthmatics. These studies showed conflicting results. Shephard and coworkers[28] investigated 14 asthmatic subjects during a 2 hour cigarette smoke exposure (24 ppm CO) and observed no significant changes in pulmonary function. Dahms et al.[29] reported on ten asthmatics, passively exposed to cigarette smoke (15–20 ppm CO) for 1 hour. The authors found a 21.4% decrease in FEV_1 following smoke exposure in asthmatics compared to normal controls. Knight and Breslin[30] studied six patients with asthma who developed an 11% decline in FEV_1 and an increase in bronchial reactivity to inhaled histamine 4 hours after a 1 hour smoke exposure (15–25 ppm CO). Wiedemann and coworkers[31] examined the acute effect of a 1 hour chamber exposure to cigarette smoke (40–50 ppm CO) on lung function and airway responsiveness in nine adult asthmatics, in whom no change in lung function, but a small decrease in nonspecific airway reactivity was observed. Recently, Stankus et al.[32] investigated the effect of a 2 hour exposure to tobacco smoke (8.7–14.1 ppm CO) in 21 patients with asthma who reported respiratory symptoms on previous exposure to cigarette smoke. In 7 of these 21 sub-

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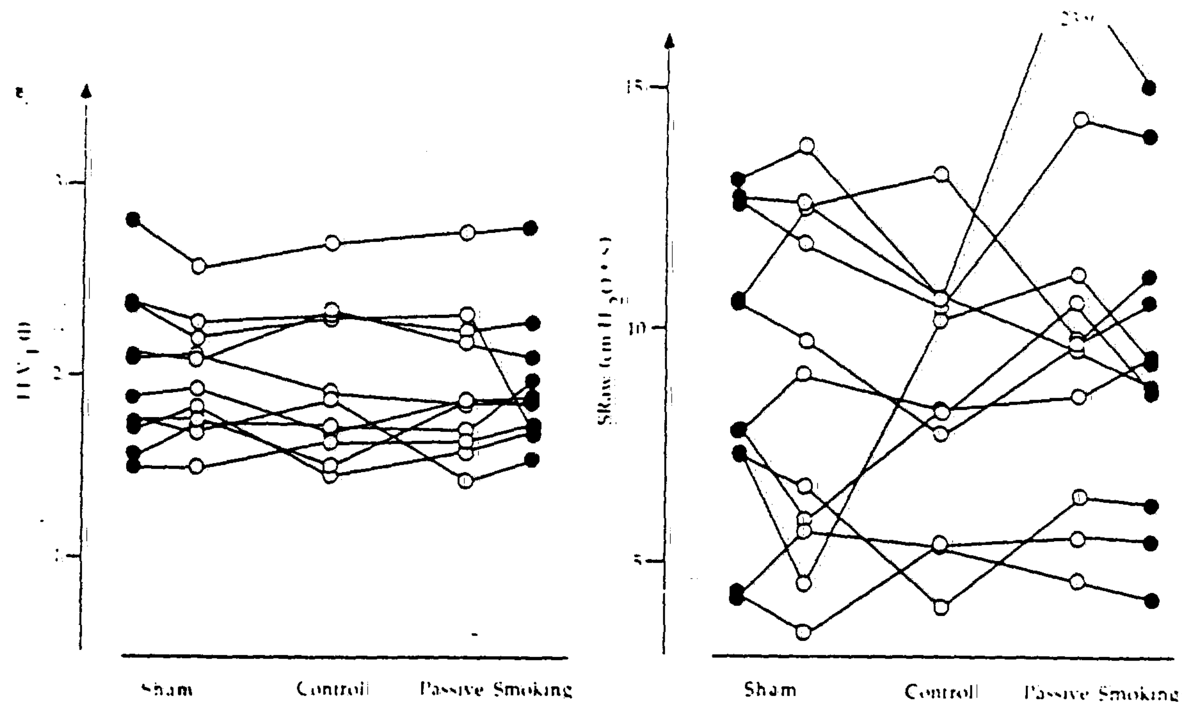

Fig. 2. FEV_1 (left) and SRaw (right) before and after exposure (Sham, passive smoking) and at the control day.

TABLE 4—Histamine Concentration (mg/mL) Necessary To Increase SRaw by 100% ($PC_{100}SRaw$) or To Decrease FEV_1 by 20% ($PC_{20}FEV_1$) After 1 Hour Exposure to Ambient Air (Sham) or Passive Smoking and at the Control Day

Patient	Control		Sham		Passive smoking	
	$PC_{100}SRaw$	$PC_{20}FEV_1$	$PC_{100}SRaw$	$PC_{20}FEV_1$	$PC_{100}SRaw$	$PC_{20}FEV_1$
1	0.25	0.09	0.51	0.27	0.30	0.21
2	0.92	0.34	5.81	0.78	6.40	1.10
3	1.60	0.73	0.38	0.11	1.24	1.05
4	1.12	1.25	2.38	0.79	1.17	0.87
5	1.45	1.72	4.59	1.68	3.16	2.64
6	2.12	1.02	3.83	1.71	6.90	3.03
7	1.07	1.13	0.59	0.60	1.45	1.57
8	0.12	0.12	0.62	0.67	1.01	1.14
9	1.85	1.28	4.80	4.22	1.40	0.75
10	0.81	0.46	0.37	0.33	0.70	0.27
11	0.66	0.30	1.24	0.68	2.79	1.00
Mean[a]	0.85	0.54	1.39	0.70	1.65	0.96
SD	2.40	2.70	3.00	2.70	2.50	2.30

[a]Geometric mean values and geometric standard deviations of mean.

jects, they found a significant (> 20%) fall in FEV_1. These findings in adult asthmatics demonstrate that there might be a subgroup of "smoke sensitive asthmatics" who develop acute airway obstruction without consistent changes in airway responsiveness following passive smoke exposure.

In our group of asthmatic children, after exposure to Sham, changes in FEV_1 between −10 and +9% were observed as compared to pre-exposure values. After passive exposure to cigarette smoke, changes of FEV_1 were within this range in nine patients. Patient no. 3 had a 13% increase in FEV_1 after smoke exposure, in contrast to a decrease of 10% after Sham. SRaw remained nearly constant both after Sham and after smoke exposure in this patient (Table 3). Patient no. 7 showed a 25% decrease in FEV_1 after smoke exposure as compared to an increase of 5% after Sham. However, there was no corresponding increase in SRaw after smoke exposure in

this patient (Table 3). Analysis of the spirometric curves did not reveal any sign of deficient cooperation in either subject. According to our study protocol, baseline lung function measurement was performed three times on three different study days. Mean coefficients of variation were 6% for FEV_1 and 21% for SRaw, which is well within the reproducibility reported in adult subjects.[33] Therefore, we do not believe that our inability to demonstrate an adverse acute effect of passive cigarette smoking on lung function was due to an insufficient reproducibility of lung function data.

Airway hyperresponsiveness to inhaled histamine in terms of $PC_{20}FEV_1$ and $PC_{100}SRaw$ was assessed three times on three different study days. The two challenges without previous smoke exposure (control, Sham) showed a variability of ± one doubling concentration of histamine, which is within accepted limits.[33,34] Therefore, it is unlikely that our findings were due to a poor reproducibility of bronchial responsiveness measurement.

Nine of 11 asthmatic children were under regular therapy with inhaled β_2-agonists and disodium cromoglycate (and in patient no. 6 with 400 µg beclomethasone diproprionate). The duration of the effect of inhaled β_2-agonists on airway tone and bronchial responsiveness lies within 3–5 hours.[35] Therefore, as we started exposure at least 6 hours after the last inhalation therapy, an influence of β_2-agonists on our data seems to be unlikely. This may, however, not be true for disodium cromoglycate (DSCG). There are conflicting data on the protective effect of DSCG on airway responsiveness. Most authors agree that a significant protection against airway obstruction induced by histamine or methacholine cannot be substantiated.[36] Recently it has been shown that long-term treatment with DSCG may modify the level of bronchial hyperresponsiveness.[37]

In our study all children showed bronchial hyperresponsiveness to inhaled histamine, irrespective of the foregoing therapy with DSCG. Three of the 9 children with DSCG showed an increase in airway responsiveness after passive cigarette smoking, and the remaining children had decreased airway responsiveness. In comparison, one child without therapy showed an increase, and the other one without therapy a decrease in hyperresponsiveness after smoke exposure. Therefore, our inability to demonstrate an effect of passive smoke exposure on airway responsiveness in hyperresponsive children is unlikely to be explained by the concomitant treatment in these patients. Nevertheless, it seems to us that in children further investigations on the possible interaction between DSCG and passive smoking are necessary.

In the present study the level of cigarette smoke exposure was characterized by several components that per se may be potential irritants. It has been suggested that substances like CO,[38] NO_2,[39] formaldehyde,[40] and aerosolized nicotine[41] may produce upper respiratory symptoms. The threshold concentration of NO_2, which causes an increase in hyperresponsiveness during resting ventilation, is about 0.25 ppm.[39] In our experiment, total NO_x concentration was about 1 ppm; however, the reactive component, NO_2 was measured to be less than 3% of the total concentration of NO_x. Acrolein (an unsaturated aldehyde) has been demonstrated to decrease pulmonary function in guinea pigs and to produce transient bronchial hyperresponsiveness, if concentrations are at least 0.31 ppm.[42,43] In our study the concentration of acrolein was in the range of 0.1 ppm. In asthmatics, exposure to saturated aldehydes like formaldehyde in concentrations up to 3 ppm for 1–1.5 hour does not cause statistically significant decrements in pulmonary function.[40,44] In our experiment, formaldehyde concentration was about 0.13 ppm. Therefore, under our conditions concentrations of the cigarette smoke components were always lower than those effective in the single component exposure studies. Because we did not see an effect of passive smoking on lung function or airway responsiveness, synergistic effects between the constituents of cigarette smoke seem to be unlikely.

By measuring urinary cotinine concentration as an accepted biological marker of chronic exposure to passive smoking,[45–48] we found elevated levels of cotinine (> 0.5 ng/mg; Table 2) in five of six children with reported smoke exposure at home. In contrast, two of five children without a positive history showed increased cotinine levels. Therefore, in most cases low urinary cotinine levels are in accordance with a history of no passive smoking, whereas elevated levels correspond to a positive history less frequently.

Since the purpose of our study was to investigate the acute effects of passive smoking and since we did not find an effect and could not identify an active component of cigarette smoke in our experiments, it is difficult to compare our data with those of chronic exposure studies. Chronic exposure has been demonstrated to increase bronchial responsiveness and to impair lung function.[10,12,13,16,17,19–23] Our data, regarding short-term exposure, are by no means contradictory to these observations. In addition, chronic passive smoke exposure may induce changes in the airways that may mask airway response to acute exposure. From our data this hypothesis cannot be proven; however, it would be of interest to study the acute airway response of asthmatic children with and without chronic smoke exposure.

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Ronchetti, R., Bonci, E., Cutrera, R., De Castro, G., Indinnimeo, L., Midulla, F., Tancredi, G., and Martinez, F.D., "Enhanced Allergic Sensitisation Related to Parental Smoking," Archives of Diseases in Childhood

The authors of this study assessed the potential role of parental smoking in changes in the prevalence and severity of the atopic state in 166 preadolescent children. The authors suggest that "this report supports the hypothesis that parental smoking is a factor that, together with specific allergenic exposure, may enhance allergic sensitisation in children."

Enhanced allergic sensitisation related to parental smoking

R Ronchetti, E Bonci, R Cutrera, G De Castro, L Indinnimeo, F Midulla, G Tancredi, F D Martinez

Abstract
The objective of this study was to assess the role of parental smoking in changes, after a four year interval (1983–7), in the prevalence and severity of the atopic state in 166 preadolescent children. Allergy skin prick tests were related to parental smoking habits and their changes during this same interval.

The total number of cigarettes smoked by parents decreased in 56 families while it increased in only 16. Boys had significantly more persistently positive skin tests and changed more frequently from negative to positive. The skin test index did not show significant changes in girls. This index did not change in children of persistent non-smokers or those starting to smoke during this period, while it increased among sons of those that quit smoking and of persistent smokers. This was not only due to those boys who became skin test positive during follow up. When analysis was restricted to 14 boys who had been skin test positive in 1983 and whose parents were persistent smokers, the index increased in eight, remained unchanged in four, and decreased in only two.

This report supports the hypothesis that parental smoking is a factor that, together with specific allergenic exposure, may enhance allergic sensitisation in children.

A significant association has been described between the prevalence of atopy in children (as assessed by skin prick tests to the most frequent allergens) and the smoking habits of their parents.[1 2] This has stimulated new interest in the study of the environmental factors that may enhance atopic expression in predisposed subjects.

Recently a very high correlation has been reported between the incidence of asthma and markers of the atopic state in a large general population sample.[3] If asthma is associated with allergic sensitisation,[3] then avoidance of factors predisposing to atopy during childhood may help prevent asthma and chronic airflow limitation later in life.

When we studied a random sample of 166 children aged 9 years, we showed that the prevalence of atopy was significantly higher in the sons of smoking parents than in the sons of non-smoking parents. We also showed, again in boys, that a prick skin test index, calculated from the combined diameters of the weals elicited by the allergens, was correlated with the total number of cigarettes smoked by their parents. We hypothesised that parental smoking, by increasing the risk of atopy, may increase the risk of asthma, particularly in their sons.[2]

Little is known about longitudinal changes occurring in skin prick test reactivity during the preadolescent years. Barbee *et al* reported that, out of 70 subjects aged 6–14 years, 15 (21·4%) had converted from initial negative to positive after a mean of 8·1 years of follow up, while 27 (38·6%) remained consistently positive, and 28 (40%) remained consistently negative. No subject became skin test negative during this age interval.[4] These investigators also reported that, paradoxically, total IgE concentrations decreased both in consistent atopic and consistent non-atopic subjects in this same age interval.[5] Factors other than the direct genetic control of IgE concentrations may play a significant part in atopic sensitisation during this crucial period of life.

The objective of this present study was to assess the role of parental smoking in changes of prevalence and severity of the atopic state in children originally enrolled at the age of 9 years. For this purpose we recalled, after a four year interval, the group of 166 subjects in whom these relationships had already been studied in 1983.[2] Allergy skin prick tests were repeated and results were related to parental smoking habits during this same interval.

Subjects and methods

Between September and November 1987 the families of all children in three Italian towns in the Viterbo province (Ronciglione, Caprarola, and Carbognano) who were previously studied at the age of 9 years in 1983, were contacted through their junior high school. Eight families had moved to other towns or could not be found. Informed consent was obtained from 142 (72 boys and 70 girls) of the remaining 158 families, a participation rate of 85·5%. There were no significant differences in health status, prevalence of positive skin tests, or parental smoking habits in 1983 between participants and non-participants in the longitudinal study.

A questionnaire, identical to that used in the previous survey, was administered to one parent. Questions on possible changes in smoking habits of each parent were added. To assess the importance of these changes, households were classified into four groups: (i) those in which there was at least one smoking parent both in 1983 and in 1987 ('persistent smokers'); (ii) those in which both parents were non-smokers, both in 1983 and in 1987 ('persistent non-smokers'); (iii) those in which at least one

IV Cattedra di
Clinica Pediatrica,
University 'La Sapienza',
Viale R Elena 324,
00161 Roma, Italy
R Ronchetti
E Bonci
R Cutrera
G De Castro
L Indinnimeo
F Midulla
G Tancredi
F D Martinez

Correspondence to:
Professor Ronchetti.

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parent smoked in 1983 and both parents were non-smokers in 1987 ('quitters'); and (iv) those in which both parents were non-smokers in 1983 and at least one parent was a smoker in 1987 ('starters'). As no difference was found in this sample between the effects of paternal and maternal cigarette smoking on skin test reactivity and bronchial responsiveness in the 1983 survey, no effort was made to differentiate these effects during follow up.[2]

Independently from this questionnaire, each child was interviewed privately by a physician regarding his/her cigarette smoking habits, after assuring the child of the confidential character of the interview. Specifically, children were asked: 'Have you ever tried to smoke cigarettes?'. If they answered affirmatively, they were asked if this had happened 'once or twice', 'seldom', or 'at least once a week'. An additional question asked them to specify the number of cigarettes smoked per week or day.

Allergy skin tests were performed using standard skin prick test methods. Extracts used were the same as those applied in our previous survey, namely house dust mites, *Alternaria tenuis* (fungus), *Aspergillus fumigatus* (fungus), *Poa pratensis* (grass), *Artemisia vulgaris* (compositae), *Parietaria officinalis* (urticaceae), *Olea europea* (olive), milk albumin, egg albumin, and cat dander. These represent the most prevalent allergens in central Italy. Operators were unaware of the results of the skin prick tests in the previous survey. The diameters of the weals elicited by the allergens (minus the diameter produced by the control solution) were summed and a skin test index was created with the following classes: class 0=0 mm, class 1=1–2 mm, class 2=3–4 mm, class 3=5–8 mm, class 4=9–16 mm, and class 5=>16 mm.

In addition, four categories of subjects were described by comparing the results of their skin tests: persistently positive, persistently negative, conversion from negative to positive, and conversion from positive to negative.

Fisher's exact test, χ^2 test, Wilcoxon's signed ranks test, and Kruskal-Wallis non-parametric analysis of variance were performed using standard Statistical Package for Social Sciences programs.[3]

Results

Table 1 shows the pevalence of current smokers among mothers and fathers of children included in this study, both for the first survey (1983) and for the present survey (1987). The percentage of non-smoking families increased from 27% to 37%. In 29 families at least one parent stopped smoking, while in 11 one parent started to smoke; in 102 there was no change in the number of smoking parents during this four year interval ($p=0.009$ by Wilcoxon's signed ranks test). Moreover, the total number of cigarettes smoked by parents decreased in 56 families while it increased in only 16 ($p<0.0001$).

Table 2 shows the numbers and percentages of boys and girls among subjects whose skin tests were persistently positive, persistently negative, changed from positive to negative, or changed from negative to positive. Boys were significantly more persistently positive (odds ratio=3·1, $p=0.03$, 95% confidence interval (CI) 1·2 to 8·1) and changed more frequently from negative to positive (odds ratio=8·7, $p=0.004$, 95% CI 1·2 to 8·2). The proportion of skin test positive girls went from 18·6% in 1983 to 15·8% in 1987, while that of skin test positive boys went from 30·6% to 43·1% during that same interval. As a consequence, mean (SD) skin test index increased significantly in boys from 0·70 (1·34) to 1·32 (1·79), with $p=0.0003$ by Wilcoxon's signed rank rest; but in girls it only increased from 0·46 (1·07) to 0·59 (1·16), $p=0.03$. Seven children (three boys, four girls) changed from positive to negative, but their mean skin test index was 1·4 in 1983—that is, their geometric mean sum of the weal sizes was only between 2 and 4 mm.

Table 3 shows the relationship between parental smoking in 1987 and changes in the results of skin prick tests by gender. In girls, there was no significant relationship between exposure to parental tobacco smoke and the results of skin prick tests performed in 1987 or changes in skin test reactivity between 1983 and 1987. However, 11/34 (32%) sons of a smoking parent became skin positive during the follow up, compared with 1/16 (6%) sons of non-

Table 1 Prevalence of smoking among parents in 1983 and in 1987. Results are number (%)

Survey	Both parents non-smokers	Father smokes only	Mother smokes only	Both parents smokers	Total
1983	39 (27)	55 (39)	13 (9)	35 (25)	142 (100)
1987	53 (37)	51 (36)	12 (9)	26 (18)	142 (100)

Table 2 Changes of skin prick test reactivity between 1983 and 1987 by sex. Results are number (%)

	Skin tests				Total
	Persistently positive	Changed from + to −	Changed from − to +	Persistently negative	
Boys	19 (26)	3 (4)	12 (17)	38 (53)	72
Girls	9 (13)	4 (6)	2 (3)	55 (78)	70
Total	28	7	14	93	142

Table 3 Relationship between parental smoking habits in 1987 and changes in skin prick tests by gender. Results in number (%)

	Skin tests				Total
	Persistently positive	Changed from + to −	Changed from − to +	Persistently negative	
Boys:					
At least one smoking parent	12 (25)	2 (4)	11 (23)	23 (48)	48 (100)
Both parents non-smokers	7 (29)	1 (4)	1 (4)	15 (63)	24 (100)
Girls:					
At least one smoking parent	5 (12)	2 (5)	2 (5)	32 (78)	41 (100)
Both parents non-smokers	4 (14)	2 (7)	0 (0)	23 (79)	29 (100)

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smoking parents ($p<0.04$ by Fisher's exact test).

When the households of the boys were classified into four groups (persistent smokers, persistent non-smokers, quitters, and starters, see methods), the parents were more likely to quit smoking between 1983 and 1987 if their sons were skin test positive in 1983. Altogether 60% (6/10) of boys belonging to families where at least one parent smoked in 1983 and none smoked in 1987 were skin test positive in 1983 compared with 7% (1/14) of atopic boys in families of persistent non-smokers ($p=0.007$ by Fisher's exact test). To avoid the confounding effect of this preferential quitting of smoking by families of atopic boys, we repeated the analysis after excluding households in which parental smoking habits had changes during the follow up period. None of 13 skin test negative sons of persistent non-smokers became skin test positive during follow up, while 11/33 (33%) sons of persistent smokers became skin test positive during follow up ($p=0.01$ by Fisher's exact test).

To assess if parental smoking was also associated with an increase in skin test reactivity, the difference between skin test index (STI; expressed in classes, see methods) in 1987 and that in 1983 (delta STI=STI87−STI83) was computed for each subject. In general, mean skin test index did not change in children of persistent non-smoking parents and significantly increased in children whose parents were persistent smokers. This increase was significantly larger in boys than in girls ($p=0.04$ by Kruskal-Wallis one way analysis of variance, ANOVA).

The skin test index did not change or become negative in girls belonging to households where parents were persistent non-smokers, starters, or quitters. Daughters of persistent smokers had higher mean skin test index than daughters of persistent non-smokers (table 4), but this difference did not reach significance ($p=0.15$ by ANOVA). Conversely (table 4), the skin test index did not change in sons of persistent non-smokers or starters, while it increased during follow up among sons of quitters and of persistent smokers ($p=0.03$ by ANOVA). This was not only due to those boys who became skin test positive during follow up; when analysis was restricted to 14 boys who were skin test positive in 1983 and who had parents who were persistent smokers, the skin test index increased in eight, remained unchanged in four, and decreased only in two ($p=0.0004$ when compared with sons of non-smoking parents).

Forty six children (32%) answered affirmatively to the question 'Have you ever tried to smoke cigarettes?' When asked more detail about these experiences, however, most ($n=31$, 22%) affirmed that this had happened only 'once or twice', while eight (6%) said they had experienced smoking 'seldom', and seven (5%) acknowledged smoking at least one cigarette a week. Only two children acknowledged smoking one cigarette a day. In this sample, these first experiences with cigarette smoking were not significantly more frequent in children of smoking parents, and the 15 children who smoked 'seldom' or 'at least one cigarette a week' did not as a group have more smoking parents than children who said they had never tried to smoke cigarettes. There was no significant effect of active smoking on prevalence of (or changes in) skin test reactivity. Exclusion of the above mentioned 15 children from the analyses did not change the results.

Table 4 Changes of skin test index during follow up by parental smoking habits and by gender

	Delta skin test index		
	Boys	*Girls*	*Total*
Persistent non-smokers:			
Mean (SD)	0·00 (0·39)	0·00 (0·92)	0·00 (0·74)
No of parents	14	20	34
Starters:			
Mean (SD)	0·00 (0·00)	1·00 (1·41)	0·40 (0·89)
No of parents	3	2	5
Quitters:			
Mean (SD)	0·50 (1·58)	−0·11 (0·78)	0·21 (1·27)
No of parents	10	9	19
Persistent smokers:			
Mean (SD)	0·87 (1·36)*	0·30 (0·95)	0·61 (1·21)**
No of parents	45	39	84

*$p=0.03$ when compared with male children of persistent non-smokers.
**$p=0.005$ when compared with children of persistent non-smokers.
Delta skin test index (STI)=STI in 1987 minus STI in 1983.

Discussion

The main finding of this longitudinal study is that, between the ages of 9 and 13 years, skin test reactivity to common aeroallergens increases significantly both in frequency and intensity in children, especially in boys, of smoking parents, while it remains unchanged in children of non-smoking parents. If we tested boys and girls separately we found no significant effect of parental smoking upon skin test reactivity in girls. These findings are in agreement with our previous report[2] of an increased prevalence of skin test reactivity to the same aeroallergens in boys but not in girls in a study of this same population sample at the age of 9 years.

It has long been known that atopy runs in families and that this is likely to be due to a genetic predisposition.[6–9] Recent studies have been implied that atopy has a dominant inheritance pattern and that the gene locus is in chromosome 11.[10] However, many environmental factors are known to modulate the phenotypical expression of this allergic predisposition. In children of atopic parents, for example, the development of allergy has been temporally associated with the incidence of viral infections.[11]

Active smoking is known to increase the incidence of allergic sensitisation to occupational exposures in otherwise non-atopic subjects. Zetterstrom *et al* showed that total IgE concentrations increased significantly in rats exposed to tobacco smoke.[12] They also reported that ovalbumin specific IgE increased significantly in smoke exposed rats when ovalbumin was administered by aerosol but not when rats were immunised against this protein by a subcutaneous route.

This present report supports the hypothesis that parental smoking is a factor that, in conjunction with specific allergenic exposure, may enhance allergic sensitisation in children. Some inaccuracy may be introduced by the self

reported questionnaire in which each subject has to establish carefully how many cigarettes he smokes. However, our data compare two successive studies in which the same parameters are operating.

It is unlikely that the reported results may be due to other factors. The study subjects belong to a stable rural population on the outskirts of Rome and among whom immigration and emigration are rare. Social status was not significantly different between parents who were smokers or non-smokers, or between persistent smokers, quitters, starters, and 'never smokers', and it is thus not likely to explain our results. It could be argued that active smoking may be more frequent in the sons of smoking parents in this age group and that this could explain our findings. However, we asked children confidentially about their smoking habits and there was no relationship between the responses to this questionnaire and changes in skin test reactivity. In addition, we had previously reported similar gender specificity in the effect of parental smoking when these children were 9 years old,[2] an age at which it is unlikely that children in our social setting could have started smoking cigarettes. Finally, Burrows *et al* reported that non-atopic subjects tended to smoke cigarettes more often than atopic subjects, while the latter tended not to start smoking and to give it up if they did begin.[13] In other words, current smokers had lower atopy rates than ex-smokers and never smokers.[13] This is opposite to our finding that sons of smoking parents tended to have higher skin test reactivity than sons of non-smoking parents.

No study has been reported that relates changes in skin test reactivity in children to parental smoking habits, and only one has dealt with the issue of longitudinal changes in skin test reactivity in children. Barbee *et al* reported that skin test reactivity increased significantly both in boys and girls between 6 and 14 and only reached a peak between 20 and 45 years of age.[4] Our studies would suggest, however, that skin test reactivity is stable between 9 and 13 years of age in girls and in the sons of non-smoking parents. In these groups, very few skin test positive subjects became skin test negative, and in those who did, the size of the initial weal was small (geometric mean of <2 mm) and perhaps clinically irrelevant.[5] In these same groups, very few subjects became skin test positive (see table 3). The situation was very different, however, for the sons of smoking parents. Almost one in four of these children became skin test positive during follow up. Barbee *et al* did not report on the influence of parental smoking or other environmental stimuli on their subjects, and it is thus not possible to compare their findings with ours.[4]

The mechanism by which environmental tobacco smoke enhances sensitisation to aeroallergens is unknown. The studies by Zetterstrom *et al* in rats suggest that a direct contact between the allergen and the bronchial mucosa is necessary for this increased sensitisation to occur.[12] This would support the hypothesis that a disruption of the bronchial epithelium by tobacco smoke with increased permeability to antigens may be involved. It is also possible, however, that the disruption of the epithelium seen in animal models of tobacco smoke inhalation may be the consequence of an inflammatory process occurring in the mucosa, which may also alter the mechanisms by which the aeroallergens are handled and presented to immunocompetent cells in the lung. Active cigarette smoke has also been found to be associated with changes in T lymphocyte function[15] and it is possible that these changes may alter the complex immunological mechanisms involved in the regulation of IgE production.[16] Experimental studies are needed to determine the relative importance of these possible mechanisms in determining an increase in allergy skin test reactivity in children of smoking parents.

As in our previous reports, we found that the association between parental smoking and allergy skin test reactivity was much more evident in boys.[2,17] We also found that boys were twice as likely to be skin test positive than girls; this was independent of parental smoking habits (table 3). One possible explanation is that our data cover a small segment of life span in which a difference in age of atopic maturation could cause differences between sexes similar to those we have found. Otherwise, as the gender distribution of atopy does not seem to be directly determined by heredity,[18] environmental factors may play a significant part in determining the difference in prevalence of atopy between genders. Boys may be more susceptible to environmental noxious stimuli and thus more prone to become sensitised to aeroallergens when their parents smoke.

A significantly higher proportion of smoking parents whose sons were skin test positive in 1983 stopped smoking between 1983 and 1987 when compared with parents of skin test negative children. This was probably due to the fact that we considered it unethical not to inform parents of the results of our previous study and these results may have induced some parents of atopic children to quit smoking.[2] It is also possible that some of these parents who quitted smoking may have been atopic themselves and thus may have been more likely both to quit smoking[13] and to have children predisposed to develop skin test reactivity. This may explain at least in part the increase in skin test index among sons of quitters (see table 4). An alternative explanation is also possible, however; early exposure (at or before the age of 9) to cigarette smoke may be more important than that occurring between 9 and 13 years in determining allergic sensitisation. Longitudinal studies including parental skin test reactivity are necessary to elucidate this issue.

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Human herpesvirus-6

Unless another one has been discovered fairly recently, there are six known human herpesviruses: herpes simplex viruses 1 and 2, cytomegalovirus, varicella zoster virus, Epstein-Barr virus, and human herpesvirus-6 (HHV-6). The latter was identified as the cause of exanthem subitum (roseola infantum) by Japanese workers in 1988.[1] Infection with HHV-6 is almost universal in young children and between 80 and 100% of young adults around the world are seropositive, but antibody titres decline after the age of 40.[2] A very high percentage of adults (more than 85% in this Californian series[2]) shed the virus in saliva and this is the presumed vehicle of infection. Exanthem subitum is, of course, usually benign but infant fatalities have been described, in Japan from fulminant hepatitis[3] and in China from haemophagocytic syndrome.[4]

A recent report, again from Japan, gives details of the virological findings in 89 infants with exanthem subitum (Yoshizo Asano and colleagues, *Journal of Pediatrics* 1991;118:891–5). They showed that children who had prolonged fever (four days or more) had significantly greater viraemia than those with a short fever (three days or less).

For a long time it has been suggested that exanthem subitum might be an important cause of febrile convulsions. Now that the virus is identified we can presumably look forward to early clarification of this relationship.

The Japanese have contributed much to modern medicine. A history of the contribution would be well worth reading.

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Ehrlich, R., Kattan, M., Godbold, J., Saltzberg, D.S., Grimm, K.T., Landrigan, P.J., and Lilienfeld, D.E., "Childhood Asthma and Passive Smoking: Urinary Cotinine as a Biomarker of Exposure," American Review of Respiratory Disease 145(3): 594-599, 1992.

The authors state that "to assess the relationship between passive smoking and asthma, we investigated (1) whether passive smoking was more prevalent among asthmatic than control children and (2) whether exposure to tobacco smoke was higher in acute asthma than in nonacute asthma." Questionnaires and urinary cotinine/creatinine ratios (CCR) were used to assess ETS exposure in 72 acute asthmatic children, 35 non acute asthmatic children and 121 control children. The authors report that acute and non acute asthmatic children did not differ in the prevalence of passive smoking at home. However, the authors report an odds ratio of 2.0 for maternal smoking and the presence of asthma. The authors conclude that "smoking by the maternal caregiver is associated with clinically significant asthma in children." However, the authors "could not show that it is a trigger of acute asthma attacks."

Childhood Asthma and Passive Smoking

Urinary Cotinine as a Biomarker of Exposure[1-3]

RODNEY EHRLICH, MEYER KATTAN, JAMES GODBOLD, DEBORAH S. SALTZBERG, KATHERINE T. GRIMM, PHILIP J. LANDRIGAN, and DAVID E. LILIENFELD

SUMMARY To assess the relationship between passive smoking and asthma, we investigated (*1*) whether passive smoking was more prevalent among asthmatic than control children and (*2*) whether exposure to tobacco smoke was higher in acute asthma than in nonacute asthma. Three groups were recruited into a case-control study: 72 acute asthmatic children from the emergency room (ER), 35 nonacute asthmatic children from the asthma clinic, and 121 control children from the ER. Both questionnaire and urinary cotinine/creatinine ratio (CCR) were used to assess passive smoking. Levels of CCR > 30 ng/mg were used to identify children exposed at home. Mean CCR was also computed. Acute and nonacute asthmatic children had similar prevalences of passive smoking at home. Acute cases showed a higher mean CCR than nonacute cases, but this was not significant. Comparing all asthmatic to control children, smoking by the maternal caregiver was more prevalent among asthmatic children (odds ratio OR = 2.0, 95% CI 1.1, 3.4). This was confirmed by CCR > 30 ng/mg (OR = 1.9, 95% CI 1.04, 3.35) and by the difference in mean CCR (43.6 versus 25.8 ng/mg, p = 0.06). We conclude that smoking by the maternal caregiver is associated with clinically significant asthma in children. We could not show that it is a trigger of acute asthma attacks.

AM REV RESPIR DIS 1992; 145:594-599

Introduction

Despite a number of epidemiologic investigations, the relation between childhood asthma and passive smoking remains uncertain. Prospective studies of general populations have failed to demonstrate an increased incidence of diagnosed asthma among the children of smokers, although an increase in parent-reported wheezing is apparent (1-5). Some cross-sectional studies have demonstrated an association between parental smoking and asthma (6, 7) or wheezing (8-10); others have failed to find such relations (11-13). In studying a group of asthmatic children, Murray and Morrison showed that maternal smoking increases the severity of the disease and bronchial hyperreactivity (14-16). An increase in the number of emergency room visits among asthmatic children from smoking households has been demonstrated in one study (17). The question of whether passive smoking triggers acute attacks of asthma has not yet been specifically addressed.

Exposure misclassification may be one reason for the inconsistency among epidemiologic studies. The studies conducted thus far have relied on questionnaire measurement of passive smoking, which may inadequately reflect the child's dose of environmental tobacco smoke. In general, exposure misclassification reduces the chances of observing a difference in asthma between exposed and unexposed children.

The aim of this study was to test two hypotheses: first, passive smoking is a risk factor for the asthmatic state, and second, recent passive smoke exposure acts as a trigger of actue attacks of asthma. To provide a more objective determination of exposure to tobacco smoke, we measured cotinine in the urine of these children. Cotinine is a metabolite of nicotine, with an elimination half-life of about 20 to 40 h (18). Among nonsmoking children, it has been shown to be correlated with maternal smoking and with the number of smokers at home (18, 19).

Methods

A case-control study was conducted from October 1988 through April 1989 in a New York City medical center. The study population comprised inner city children aged 3 to 14 yr attending the pediatric emergency room (ER) or the pediatric asthma clinic at the hospital. The ER functions as both a walk-in clinic and an emergency room.

Cases of acute asthma were ascertained from children presenting to the ER on weekdays. The definition of a case of actue asthma required (*1*) a physician diagnosis in the ER of acute airflow obstruction requiring bronchodilator therapy, and (*2*) at least one previous episode of physician-diagnosed acute asthma as reported by the accompanying adult.

A second case group, consisting of children whose asthma was not acute, was recruited from all children aged 3 to 14 yr attending the asthma clinic during the period of study. These children all had a history of episodic or chronic airflow obstruction requiring some form of bronchodilator therapy. Any child (*1*) who had suffered an attack of acute asthma resulting in a visit to a doctor or school absence during the previous 2 wk or (*2*) who required treatment during that visit to the clinic was excluded.

The control group comprised children attending the ER during the period of the study with any presentation other than acute asthma. The accompanying adult was interviewed about demographic characteristics (age of child, sex, ethnic group, parental occupation, and years of schooling completed by parents), pets, recent history of asthma and other illness (including recent upper respiratory infection), use of asthma medication, and smoking habits of the maternal caregiver (mother or other primary caregiver) and oth-

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[1] From the Division of Environmental and Occupational Medicine, Department of Community Medicine, and the Jack and Lucy Clark Department of Pediatrics, Mount Sinai Medical Center, New York, New York.

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[3] Correspondence and requests for reprints should be addressed to Rodney Ehrlich, M.D., Department of Community Medicine, University of Capetown Medical School, Observatory 7925, South Africa.

er household members. Gas stove use was not included because a pilot study found gas use to be almost universal in this population. Children aged 10 to 14 yr were taken aside by the interviewer, who inquired whether the child had ever tried smoking, and if so, whether he or she had smoked recently. Chart review was undertaken to exclude subjects who did not meet study criteria and to determine asthma medication.

An upper respiratory infection (URI) was defined as the occurrence during the previous week of any two of a list of four symptoms. These included (*1*) a runny nose not "usual" nor "frequent" for that child (to distinguish acute infecton from allergic symptoms), (*2*) sneezing, also not usual nor frequent, (*3*) sore throat, and (*4*) sore or discharging ears. Alternatively, if the adult reported fever in the child or a cold in another household member in the previous week, only one of the four symptoms was needed to define a URI.

Noncompliance was defined as having missed one or more doses of asthma medication during the previous week if the child was on a prescribed daily regimen. An index of socioeconomic status (SES) was computed from the occupational category and years of education of the parent(s) with whom the child resided (Hollingshead AB. Four factor index of social status. Department of Sociology, Yale University, 1975). Parents or guardians were classified into three categories: (*I*) unskilled, semiskilled, or not formally employed; (*II*) skilled, clerical, or sales; or (*III*) technical, professional, or business. The 6 months of the study were classified by average monthly temperature (recorded by the New York Meteorological Service) into cool months (October, November, and April) or cold months (December, February, and March).

The smoking status of the maternal caregiver (current, ex, or never) and of each household member (current or not) was recorded. Number of cigarettes smoked daily was coded into four intervals (1 to 5, 6 to 15, 16 to 20, and > 20). The total number of cigarettes smoked daily by all household smokers was expressed as a continuous variable by summing representative numbers for each of the four intervals (2, 10, 20, and 25, respectively).

A urine specimen was collected from each child at the time of the interview. Within 2 h it was deep frozen until transfer to the laboratory. Urinary cotinine concentration was determined by competitive inhibition radioimmunoassay using rabbit cotinine antiserum and tritiated cotinine (20). To adjust for the effect of variable dilution on the spot concentration of cotinine, urinary creatinine was measured and the cotinine/creatinine ratio (CCR) was calculated.

Because the frequency distribution of the CCR values was highly nonnormal, being skewed to the right, CCR values were analyzed in two ways. First, Henderson and colleagues (21) reported that a cutoff CCR level of 30 ng/mg identifies children exposed at home with a high degree of sensitivity (80%) and specificity (100%). This level was therefore used to categorize subjects into exposed and unexposed. Second, logarithmic transformation of CCR produced a bimodal distribution with one peak at the zero or nondetectable level and a log normal distribution of the remaining values. Owen and DeRouen (22) have shown that a function proposed by Aitchison (the Aitchison estimator) provides best estimates of the mean and variance of such a distribution. These statistics were estimated for grouped CCR values and a z test applied to differences between groups.

The role of possible confounding or effect-modifying variables, such as age, sex, and ethnicity, were examined by stratified analysis. (Effect modification refers to significant variation of the odds ratio with different levels of a third variable, such as sex. For example, the association between passive smoking and asthma might be observed among boys but not among girls). Multivariate analysis was performed using the BMDP statistical software for logistic regression via SAS (SAS Institute Inc., Release 5.18, March 1989).

This study was approved by the institutional review board of the hospital, and informed consent was obtained for each participant.

Results

A total of 271 parents or guardians were approached in the ER and asthma clinic, of whom 244 (90%) gave informed consent. Response rates by group were acute asthma (88%), asthma clinic (98%), and ER control (88%). Fourteen asthmatic and two control subjects were rejected on chart review for failing to meet study criteria (e.g., no previous asthma among acute asthmatic cases or an attack in the prior 2 wk among clinic cases). This left 228 children in the study: 72 acute asthmatic children, 35 children from the asthma clinic, and 121 ER control children. Urine was not obtained from 14 of these, leaving 214 for cotinine analysis. The mother was the study respondent for 181 children (79%); for the remainder the father, grandmother, or aunt provided the information. For 18% of children, someone other than the biologic mother was the primary caregiver, usually the grandmother. In 55% the father did not live at home. Among the controls, 35% had respiratory diagnoses identified on chart review (including ear, nose, and throat), 8% "viral syndrome" and 12% trauma or soft tissue diagnoses; 45% had other medical diagnoses (abdominal, eyes, skin, neurologic, others), including some with no clear diagnosis.

TABLE 1

ACUTE VERSUS NONACUTE ASTHMA: SAMPLE CHARACTERISTICS

Factor	Acute Asthma (n = 72)	Nonacute Asthma (n = 35)
Age, yr	7.0 (3–14)	7.9 (3–14)
Sex (male), %	63	60
Ethnicity, %		
Hispanic	60	66
African-American	37	26
Other	3	9
SES, %*		
I	63	66
II	18	20
III	19	14
URI, %*	69	47†
Previous use of ER for acute asthma, %	97	86‡
Any previous attendance at asthma clinic, %	65	100§
Daily asthma medication, %	36	80§
Missed any dose in previous weeks*, %	16	14

* See text for definition.
† Odds ratio (OR) = 2.5 (1.1, 5.6); p = 0.03.
‡ p = 0.02.
§ p = 0.000.

Acute Versus Nonacute Asthmatic Children

Demographic and medical features of acute asthma and nonacute asthma are displayed in table 1. The two groups were similar in age, sex, and SES. African-American children were overrepresented in the acute group. Recent URI was markedly more common among the acute asthmatic children, with an odds ratio (OR) of 2.5 (95% confidence interval, 1.1, 5.6).

With regard to pattern of medical care, most of the children in both groups previously made use of the ER for acute asthma. A smaller percentage (65%) of the acute asthmatic children previously attended the asthma clinic. Among those children on a daily medication regimen, there was no difference in the proportions missing one or more doses in the previous week. However, the asthma clinic

TABLE 2

ACUTE VERSUS NONACUTE ASTHMA: EXPOSURE VARIABLES

Factor	Acute Asthma (n = 72)	Nonacute Asthma (n = 35)
Any smoker at home, %	53	57
Daily cigarettes by all smokers, mean ± SD (standard deviation)	7.7 ± 11.8	10.7 ± 14.6
Maternal caregiver currently smokes, %	40	51*
CCR ≥ 30 ng/mg, %	38	39†
Mean CCR, ng/mg, %‡	46.2 ± 98.3	38.5 ± 74.1§
Hispanic	40.9 ± 13.3	34.4 ± 14.7
African-American	57.4 ± 28.9	59.2 ± 41.7

* Odds ratio = 0.6 (0.28, 1.43), $p = 0.2$.
† Odds ratio = 0.9 (0.38, 2.19); $p = 0.8$.
‡ Aitchison transformation: see METHODS.
§ $p = 0.66$

TABLE 3

ASTHMA VERSUS CONTROL: SAMPLE CHARACTERISTICS

Factor	Asthma (n = 107)	Control (n = 121)
Age, yr	7.3 (3–4)	7.5 (3–14)
Sex (male), %	62	59
Ethnicity, %		
Hispanic	62	72
African-American	34	28*
Other	5	1
SES, %†		
I	64	66
II	19	19
III	18	15
URI, %†	62	62
Month, %		
October/November/April (cool)	55	40‡
December/February/March (cold)	45	60

* $p = 0.08$.
† See text for definition.
‡ $p = 0.02$.

TABLE 4

ASTHMA VERSUS CONTROL: EXPOSURE VARIABLES

Factor	Asthma (n = 107)	Control (n = 121)
Any smoker at home, %	54	51
Daily cigarettes by all smokers, mean ± SD	8.7 ± 12.8	6.1 ± 10.3
Maternal caregiver smokes, %	44	28*
CCR ≥ 30 ng/mg, %	38	25†
Mean CCR, ng/mg‡	43.6 ± 87.7	25.8 ± 46.5§

* Odds ratio = 2.0 (1.1, 3.4), $p = 0.03$.
† OR = 1.9 (1.04, 3.35); $p = 0.04$
‡ Aitchison transformation, see METHODS
§ $p = 0.06$

group had a much larger proportion on such a daily regimen. There was no difference between the groups in pet ownership or month of recruitment.

The passive smoke exposure of the two groups is compared in table 2. There was no significant difference in general household smoking. Smoking by the maternal caregiver was more common in the nonacute group. There was no difference in the proportions of children exposed at home as defined by CCR levels at or above 30 ng/mg. The mean CCR was nonsignificantly greater in the acute group (46.2 ng/mg) than among the nonacute children (38.5 ng/mg).

Because the two asthma groups were similar with regard to demographic characteristics, smoking prevalences, and past ER use, they were combined into a single asthmatic group for comparison with the control group.

Asthmatic Versus Control Groups

The asthmatic and control groups are similar with respect to age, sex, SES, and recent URI, as shown in table 3. There was a significant difference in month of recruitment, with asthmatics enrolled in higher proportion than control subjects in the cool months of October, November, and April compared with the cold months. There was also a greater proportion of African-American children among those with asthma. There was no difference in ownership of household pets.

Comparing smoking variables (table 4), there was no significant difference in the proportions having any smokers at home or in daily cigarette consumption by all smokers. The maternal caregiver, however, was much more likely to smoke among the asthmatic group (OR = 2.0). This was confirmed by the differences in CCR, whether defined categorically (OR = 1.9) or quantitatively (mean 43.6 versus 25.8 ng/mg).

When analysis was restricted to those children ($n = 181$) whose maternal caregiver was their biologic mother, the same association between maternal smoking status and asthma was found. This was so whether maternal smoking was defined as (*1*) current smoking by the biologic mother [OR = 1.9 (95% confidence interval 1.1, 3.6)], (*2*) current or exsmoking [OR = 2.0 (1.1, 3.8)], or (*3*) smoking in pregnancy [OR = 1.9 (1.1, 3.5)].

Ethnicity and month of recruitment were examined as potential confounders. African-American children had a slightly higher mean CCR (38.9 ± 9.4 ng/mg) than Hispanic children (32.6 ± 5.16 ng/ml), and they showed no significant difference on the categorical CCR measure [OR = (0.7–2.5)].

Regarding month of recruitment, there was no difference in CCR between the cool and cold months, whether measured categorically or quantitatively. On entering CCR (≥ 30 ng/mg), month, and ethnicity simultaneously into a logistic regression model, the association between CCR and asthma was altered only slightly, increasing the odds ratio from 1.9 to 2.0.

Boys showed a stronger association between maternal smoking and CCR (≥ 30 ng/mg) and their asthma than did girls. The differences were not statistically significant, however.

To remove the influence of extreme values, the analysis was repeated excluding the three CCR outliers greater than 200 ng/mg. The results were essentially unchanged.

The analysis was repeated using only acute asthmatic subjects as the case group (table 5). The pattern was similar to that of table 4, except that the odds ratios were slightly smaller, and no longer significant at the 0.05 level, for the comparison of

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TABLE 5

ACUTE ASTHMA VERSUS CONTROL: EXPOSURE VARIABLES

Factor	Acute Asthma ($n = 72$)	Control ($n = 121$)
Any smoker at home, %	53	51
Daily cigarettes by all smokers, mean ± SD	7.7 ± 11.8	6.1 ± 10.3
Maternal caregiver smokes, %	40	28*
CCR ≥ 30 ng/mg, %	38	25†
Mean, CCR, ng/mg‡	46.2 ± 98.3	25.8 ± 46.5§

* Odds ratio = 1.7 (0.92, 3.15), $p = 0.08$.
† Odds ratio = 1.8 (0.94, 3.50), $p = 0.07$.
‡ Aitchison transformation, see METHODS.
§ $p = 0.11$

maternal smoking and CCR measured categorically. The mean difference in CCR between acute asthmatic and control children was 46.2 versus 25.8 ng/mg, was also non-significant.

The association of CCR (≥ 30 ng/mg) with questionnaire measures of exposure was computed. CCR was most strongly associated with the maternal caregiver's smoking status [OR = 11.9 (6.3, 22.3)]. Association with smoking by household smokers other than the maternal caregiver was lower [OR = 3.4 (1.3, 8.7)]. To examine further whether smoking by the maternal caregiver was mainly a surrogate for the total number of smokers in the home, the correlation of smoking by maternal caregiver with number of other smokers was calculated. There was little correlation (Spearman's coefficient = 0.1; $p = 0.13$). CCR thus accorded most closely with current smoking by the maternal caregiver as an independent source of passive smoking by the child.

None of the children questioned admitted to smoking. Active smoking by the child could be a confounder of the association between passive smoking and asthma. If recent, it should account for CCR levels at the high end of the distribution. These possibilities were explored by examining the characteristics of those children with high CCR values (> 100 ng/mg) (table 6). The ages of these children were mostly at the low end of the age range, making it highly unlikely that active smoking explains most of these values. Further, they were evenly divided between cases and controls, so that even if all were attributable to active smoking the error would not be systematic.

Discussion

We found that passive smoking is associated with clinically significant childhood asthma in a sample of children drawn from an inner city population of mainly Hispanic and African-American children using a hospital's ambulatory care services.

The comparability of the groups needs to be considered. Controls in our study were drawn from the pediatric ER and can be regarded as sampling the population of children who use the ER. There were no confounding demographic differences between control and asthmatic children. The asthma clinic subjects, although not drawn from the ER, previously used the ER in 86% of cases, making it unlikely that they differed markedly from acute asthmatic or control children in their pattern of use of the ER for acute illnesses.

Among children using the ER with diagnoses other than acute asthma, a large proportion present with respiratory symptoms. Passive smoking has been shown to be associated with acute respiratory infection in younger children and chronic respiratory symptoms in older children (23). Our control group therefore probably had more passive smoke exposure than would be found in a comparable group of community controls. If so, we would be less likely to observe a difference in passive smoking between control and asthmatic children in this study. The fact that an effect was nonetheless found strengthens its validity.

Smoking by the maternal caregiver was the exposure variable most strongly associated with the asthmatic state. There is now evidence from a number of studies that it is maternal smoking that is important in predicting the risk or severity of asthma or wheezing (4–7, 9, 14–16). In our study we were unable to distinguish among current or past smoking by maternal caregiver or smoking in pregnancy by the biologic mother, as these measures were closely intercorrelated and all significantly associated with the child's asthmatic status. However, we confirmed that this is a direct effect of maternal smoking rather than a reflection of the number of smokers in the household.

We were unable to show an effect of passive smoke exposure on the precipitation of acute asthmatic attacks. For this purpose, we distinguished children visiting the ER with an acute attack at the time of recruitment from children with presumed similar asthmatic conditions who were not acute. We found no difference between the acute and nonacute groups when the CCR was used as a categorical measure (OR = 0.9), and self-reported smoking by the caregiver was actually more common among the nonacute group (OR = 0.6). Using CCR as a continuous variable, an elevation in the acute group was non-significant (46.2 versus 38.5 ng/mg).

The power of this second part of the study to show a twofold excess of exposure among acute asthmatic subjects

TABLE 6

SUBJECTS WITH COTININE/CREATININE RATIO > 100 NG/MG

CDR	Age (yr)	Maternal Caregiver Smokes	Other Smokers at Home
Asthma			
745	3	No	Yes
335	5	Yes	Yes
270	4	No	No
238	3	No	No
186	5	Yes	No
140	3	Yes	Yes
118	9	Yes	Yes
Control			
468	3	Yes	No
232	5	No	No
136	7	Yes	No
130	5	Yes	Yes
128	8	No	Yes
112	12	No	No
102	9	Yes	Yes

was less than 50%. However, conjecture that a larger sample might have shown such a significant positive association must be balanced against what was observed: no difference at all between the two groups with regard to cotinine measured categorically, and a negative association between maternal smoking status and acute asthma.

There were also some differences between the two asthmatic groups, which may have made it more difficult to show a positive association. Among the acute cases, only 65% had at some time previously attended the asthma clinic. Further, only 34% were on daily asthma medication at the time of recruitment compared to 80% of the asthma clinic cases. It is therefore possible that children attending the asthma clinic have more severe asthma. If greater severity of asthma is itself associated with passive smoking (14–16), the asthma clinic group may have had more passive smoke exposure to begin with. This would make it more difficult to show an elevated CCR in the acute asthma group even if they were subject to recent increases in exposure. It is possible that a real effect was thereby obscured. An alternative possibility is that treatment suppresses the effect of passive smoking. In such a case, the triggering effect of such exposure may be evident only in comparing acute cases with nonacute cases among children not on regular medication. Our numbers were too small to explore this further.

Use of cotinine as a biomarker of exposure enabled us to validate the reported smoking status of the maternal caregiver and to demonstrate nicotine absorption by the child. In addition, it provided an exposure measure free of interviewer bias.

The use of cotinine raised methodologic questions that need to be resolved. Other studies have shown that cotinine is measurable, sometimes at high levels, in children with no reported exposure at home (19). We found this also. We made use of the findings of Henderson and colleagues (21), who found that a cutoff level of 30 ng/mg optimally distinguished children exposed to tobacco smoke at home (measured by air nicotine concentration and cigarette butts saved) from those unexposed.

We used cotinine to measure degree of recent exposure among acute and nonacute asthma. This presupposes that cotinine levels reflect the intensity of passive smoking. Because of interindividual differences in metabolism, however, the variation in cotinine among children for a given exposure may be considerable. It also remains to be confirmed whether urinary cotinine levels in an individual child are stable over time so that a single measure reflects "average" exposure, or whether they are sufficiently sensitive to changes over and above this background exposure level to detect short-term ("peak") increases. Henderson's group, doing repeated measures, found stable urinary CCR levels over a period of 4 wk (21). The correlation coefficient found between average log CCR and average home nicotine concentration was 0.68. In contrast, Coultas and coworkers reported a wide variation in urinary CCR over a period of about 11 wk; their correlation coefficient between CCR and ambient nicotine was 0.15 (24). In view of the difficulties posed by these conflicting data, the hypothesis concerning acute exacerbation of asthma by environmental tobacco smoke needs a prospective study of asthmatic children, linking acute exacerbations of asthma to variations in exposure based both on repeated measures of cotinine and on some measure of environmental exposure.

We conclude that passive smoking by the mother or other maternal caregiver is associated with the asthmatic state among children. Given our observed odds ratio around 2.0, the high prevalence of both parental smoking and asthma makes this association a public health problem of considerable impact in this population.

We could not show that recent elevations in exposure to tobacco smoke triggered attacks of asthma requiring visits to the emergency room. Lack of statistical power, differences between acute and nonacute cases in medication use, and limitations in using a single cotinine measure may explain this finding rather than a true lack of effect. If our finding is valid, however, it may be because the mechanism of effect of maternal smoking on asthma is through increasing bronchial responsiveness in the child rather than by triggering bronchospasm. A number of studies have shown that bronchial responsiveness among asthmatic children is greater if the mother smokes (14–16, 25, 26). Such a mechanism is also compatible with the finding of Evans and colleagues (17) that the number of ER visits for acute asthma is increased if there is a smoker in the household. In contrast to these findings, those of general population studies have yet to clearly demonstrate an association between bronchial responsiveness in children and parental smoking (25, 26).

The clinical implications of this study are clear. Maternal smoking in the households of asthmatic children in this population is all too common. Reduction of this potentially important risk factor should be the target of clinicians and health educators working with the families of these asthmatic children.

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Murray, A.B., and Morrison, B.J., "Effect of Passive Smoking on Asthmatic Children Who Have and Who Have Not Had Atopic Dermatitis," Chest 101(1): 16-18, 1992.

The authors of this study examined 240 children aged 6-17 years who had been referred consecutively to their clinic. They report that "multiple analysis of variance revealed that children whose mothers smoked had significantly more severe asthma but that atopic dermatitis had no apparent effect on the severity of asthma, either in its main effect or in its interaction with maternal smoking." The authors conclude that "in smoking mothers' children the asthma was just as severe in those who had not had atopic dermatitis as in those who had."

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Effect of Passive Smoking on Asthmatic Children Who Have and Who Have Not Had Atopic Dermatitis*

Andrew B. Murray, M.B.;† and Brenda J. Morrison, Ph.D.‡

We studied 240 children with asthma who were themselves nonsmokers and had been referred consecutively to our clinic. They were aged 6 to 17 years. The severity of asthma was assessed by symptom score, by spirometry, and, in those who could perform the test reliably, by histamine bronchial challenge test. Those who reported having had a chronic or chronically relapsing itchy rash in characteristic locations were recorded as having had atopic dermatitis. Multiple analysis of variance revealed that children whose mothers smoked had significantly more severe asthma ($p \leq 0.001$) but that atopic dermatitis had no apparent effect on the severity of asthma, either in its main effect ($p = 0.71$) or in its interaction with maternal smoking ($p = 0.66$). Although our previous study indicates that smoking mothers' children are more likely to develop asthma if they have had atopic dermatitis than if they have not, the severity of asthma does not appear to be associated with a history of atopic dermatitis. In smoking mothers' children the asthma was just as severe in those who had not had atopic dermatitis as in those who had. *(Chest 1992; 101:16-18)*

MANOVA = multiple analysis of variance; PC_{20} = provocation concentration of histamine required to decrease FEV_1 by 20 percent

Smoke pollution in the home appears to aggravate symptoms in children with asthma. In our first study population, which comprised the asthmatic patients who attended our allergy clinic, we found that asthmatic symptoms were more severe, and that pulmonary function test results were lower in those whose mothers were smokers than those whose mothers were nonsmokers.[1-3]

Not only does passive smoking appear to exacerbate symptoms in those who are already asthmatic, there is also strong evidence that it causes asthma in certain children who would not otherwise have had this disease. This was found in a second study population, one that included all of the children who attended our allergy clinic. We demonstrated that children with atopic dermatitis were much more likely to have asthma if the mother smoked than if she did not smoke.[4] In those with no history of atopic dermatitis, by contrast, asthma was just as frequent in those with a nonsmoking mother as in those with a mother who smoked.

This finding, that passive smoking is a risk factor for causing asthma only in the children who have a history of atopic dermatitis, raises the question as to whether it is also solely asthmatic children with atopic dermatitis whose asthma is aggravated by smoke pollution in the home. Knowing the correct answer to this question is necessary to answer the following one: should smoking parents of an asthmatic child be counselled just as forcefully about smoke avoidance if the child has never had atopic dermatitis as when the child has had atopic dermatitis?

In order to answer these questions, we reanalyzed the data from our first study.[2] A history concerning the presence or absence of atopic dermatitis was available on all but three of the children who had comprised the earlier study's population.

Materials and Methods

The population and some of the methods were described in detail in an earlier publication.[2] In brief, the series included every child who had a history of asthma or frequent wheezing, who was aged 7 to 17 years, who had been referred to one of us (A.B.M.) at the Children's Hospital Allergy Clinic in Vancouver, and who was seen between Nov 1, 1983 and May 31, 1986. The data recorded at the first visit during this period were used in the study. There were 247 subjects in all.

Questionnaire

A trained interviewer put standardized questions to the patient and to the accompanying adult who, in 97 percent of the cases, was a parent. The parents or the accompanying person was asked how long the child had had the asthma or wheezing,[5] whether the child had suffered from a cold or respiratory infection during the preceding two weeks, and whether the child had received a medication which might affect the result of the histamine bronchial challenge test.[2] They were also asked how severe they considered the child's asthma to be, how frequently the child had wheezed and had received medication during the previous 12 months, whether corticosteroids had been given, and whether there was wheezing on exertion. Each of these features was assigned a numeric score indicating severity, and the sum of these numbers was the asthma symptom score.[1,3,6] In addition, parents were asked whether the child had ever had a rash and, if so, whether it had been itchy, how

*From the Departments of Paediatrics, and of Health Care and Epidemiology, University of British Columbia, Vancouver, Canada.
Supported in part by a grant from the British Columbia Lung Association.
Manuscript received November 5, 1990; revision accepted April 25.
†Professor of Paediatrics.
‡Associate Professor of Health Care and Epidemiology.
Reprint requests: Dr. Murray, 4480 Oak Street, Vancouver, BC V6H 3V4

long it had lasted, and what its distribution had been. Only children who had had a rash which was itchy, which was chronic or chronically relapsing, and which had occurred in characteristic areas were classified as having had atopic dermatitis.[7]

When the previous questions had been completed, the parent or accompanying adult was asked whether the mother smoked and whether the father smoked.[3] The child was asked privately whether he or she smoked. The four children who admitted to being smokers were excluded from the study.

Forced Expiratory Spirogram

Forced expiratory maneuvers were performed until there were three in which the forced vital capacity (FVC) agreed within 5 percent. Three children who were unable to perform consistently satisfactory spirograms were eliminated from the series. The forced expiratory volume in one second (FEV_1) and the forced expiratory flow during the middle half of the FVC (FEF25-75%) were expressed as a percentage of the predicted mean for age, sex, and height.[8]

Bronchial Responsiveness to Histamine

Parents were contacted by telephone 48 hours prior to the appointment and were instructed to discontinue medications which might influence a bronchial challenge test. After the spirogram had been recorded, a bronchial challenge test was given to all of the 103 children who could perform the test reliably; that is, it was given to all except those who had recently taken medications which might interfere with the test[8] or had had a respiratory infection within the previous two weeks or had a FEV_1 which was less than 60 percent of predicted.

Aerosol histamine was administered by mask using the method of Cockcroft et al.[2,9] Children whose FEV_1 did not decrease by 20 percent when the strongest concentration (8 mg/ml) was administered were deemed, for the purpose of calculating the PC_{20}, to respond to double that concentration, *ie*, 16 mg of histamine acid phosphate per milliliter.

Statistical Analysis

There were 240 subjects, 206 of whom had data concerning all of the dependent and independent variables (other than PC_{20}, which was recorded in a subset of 103). Of the 206 subjects, 46 had smoking mothers, and 160 did not; 62 had had a recent respiratory infection, and 144 had not; and 79 had had atopic dermatitis, and 127 had not. Previous analysis of these patients[1-3] by multiple regression had indicated that the most important predictors of the severity of asthma were maternal smoking, recent respiratory infection, age, and the age of onset of asthma. A MANOVA test was therefore carried out using the following as dependent variables: FEV_1%; FEF25-75%; and asthma symptom score. The design consisted of a $2 \times 2 \times 2$ factorial analysis incorporating all possible interactions. The factors were whether or not the child had had atopic dermatitis, whether or not the mother smoked, and whether or not the child had had a recent respiratory infection. Age and the age of onset were used as covariates.

In a previous analysis, smoking by the father was found to be a predictor of the severity of asthma in boys only and not in the population as a whole; this variable was therefore not included in the MANOVA.[3]

The PC_{20} measurement was not included as a dependent variable because none of the children with a recent respiratory infection was given a histamine bronchial challenge test, the reason for omitting this test being that infection is thought to aggravate bronchial responsiveness.[9] Therefore, for PC_{20}, a separate two-factor analysis was run, with maternal smoking and atopic dermatitis as factors; and since age and the age of onset were not found to be predictive, analysis of variance, rather than analysis of covariance, was performed.

Table 1—*Adjusted Means of Measures of Severity of Asthma**

Measure	Maternal Smoking		Recent Respiratory Infection		Atopic Dermatitis	
	No	Yes	No	Yes	No	Yes
Asthma symptom score	6.9	9.1	7.4	8.6	7.9	8.1
FEV_1, percent of predicted	84.0†	76.5†	82.2‡	78.3‡	79.4§	81.2§
FEF25-75%, percent of predicted	71.0	59.2	68.9	61.3	62.8	67.4
ln PC_{20}‖	0.7¶	−0.1¶	...	...	0.4**	0.2**

*Adjusted for covariates, age and age of onset, and for two of the factors, maternal smoking, recent infection, and atopic dermatitis.

†p = 0.001.

‡p = 0.008.

§p = 0.71.

‖These means were adjusted by factors, maternal smoking and atopic dermatitis; no covariates were used.

¶p = 0.008.

**p = 0.40.

Results

When considering the main effects of the factors in the MANOVA analysis, children whose mothers smoked were found to have significantly more severe asthma than those whose mothers did not smoke ($p = 0.001$; see Table 1). In contrast, atopic dermatitis and recent respiratory infection had no apparent effect on the severity of asthma, either as main effects, or as a result of their separate or combined interactions with maternal smoking; however, the covariates, age and age of onset, were found to be highly significant predictors of the severity of asthma.

The analysis of the PC_{20} levels produced similar findings. The levels were significantly different in the children of the smoking mothers as compared with those of nonsmoking mothers ($p = 0.008$), but a history of atopic dermatitis was not predictive of the PC_{20} levels ($p = 0.404$).

Discussion

We had observed in another study that children in our clinic had asthma more frequently if the mother smoked than if she did not smoke, but that this increased frequency of asthma was limited to those who had had atopic dermatitis.[4] This finding raised the following question: was the aggravation of asthma in asthmatic children of mothers who smoked, as reported by us in our clinic patients[1-3] and confirmed by others in community surveys,[10,11] also confined to those who had had atopic dermatitis? It was in order to answer this question that we reanalyzed the information collected during our earlier study,[2] the one which had been performed on a clinic population of asthmatic children.

Our analysis reconfirmed that asthmatic children who had smoking mothers had more severe asthma

than those who did not, whether judged by the severity of symptoms or by pulmonary function testing, and it indicated that this aggravation of their asthma was not confined to those who had had atopic dermatitis; atopic dermatitis was not a predictor of the severity of asthma, either on its own, or combined with maternal smoking.

Our data did not confirm that recent respiratory infection was a predictor of increased severity of asthma. Even though the number of subjects was substantial, neither the main effect of recent infection, nor its interaction with atopic dermatitis or maternal smoking achieved statistical significance. Nevertheless, there is a possibility that in some subgroups of children, recent infection might be important in determining the severity of asthma.

It is not likely that children were incorrectly classified as nonsmokers themselves when they did in fact smoke. Using a carbon monoxide monitor, we have measured the CO content in the expired air of consecutive patients who were aged between 9 and 17 years and who were seen subsequently.[12] Only the two who admitted to being smokers had a CO concentration above 8 ppm; the other 77 who claimed to be nonsmokers all had a CO concentration below this level (unpublished data). These findings suggest that the children who attend our clinic are truthful about their smoking habits, as has been found in children in London[13] and New York.[14]

Although passive smoking may cause asthma only in children who have had atopic dermatitis,[4] we conclude that smoke aggravates asthma in those who have not had atopic dermatitis as well as in those who have. It is therefore appropriate to urge parents of all asthmatic children, even those who have not had atopic dermatitis, to refrain from smoking when in the house or when in the car with the child.

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Frischer, T., Kuehr, J., Meinert, R., Karmaus, W., Barth, R., Hermann-Kunz, E., and Urbanek, R., "Maternal Smoking in Early Childhood: A Risk Factor for Bronchial Responsiveness to Exercise in Primary-School Children," Journal of Pediatrics 121(1): 17-22, 1992.

The authors examined the possible relationship between maternal smoking and bronchial hyperresponsiveness in a cohort of 1812 primary-school children in first grade. A standardized free running test was performed on the children. Exposure to maternal smoking was estimated via questionnaire information. The authors reported that bronchial hyperresponsiveness was more common in children of smoking mothers. They reported odds ratios of 2.82 (95% CI: 1.25-6.34) for children reportedly exposed to maternal smoking in the first year of life and 20.55 (95% CI: 2.5-168.9) for asthmatic children reportedly exposed to maternal smoking in the first year of life. However, "current exposure to maternal smoking was associated with less hyperresponsiveness."

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Maternal smoking in early childhood: A risk factor for bronchial responsiveness to exercise in primary-school children

T. Frischer, MD, J. Kuehr, MD, R. Meinert, MSc, W. Karmaus, MD, MPH, R. Barth, MD, E. Hermann-Kunz, MD, and R. Urbanek, MD

From the University of Children's Hospital, Freiburg im Breisgau, the Bundesgesundheitsamt, Berlin, and the Nordig Institut fuer Gesundheitsforschung, Hamburg, Germany; and the University Children's Hospital, Vienna, Austria

The relationship between maternal smoking and bronchial hyperresponsiveness as assessed by a standardized free running test was investigated in a cohort of 1812 primary-school children in first grade. A child's exposure to maternal smoking during pregnancy, the first year of life, and the study year was recorded. Current exposure was not positively associated with bronchial hyperresponsiveness. The prevalence of this disorder was higher when maternal smoking ...ring the child's first year of life was reported (9%) than when it was not (5.9%). ...e odds of being hyperresponsive were significantly higher in children exposed ... maternal smoking in their first year of life (odds ratio, 2.82; 95% confidence ...erval, 1.25 to 6.34; p <0.01), especially in children with asthma (odds ratio, ...0.55; 95% confidence interval, 2.5 to 168.9; p <0.01). Current exposure to maternal smoking was associated with less hyperresponsiveness. The effect of current maternal smoking might reflect changes in smoking habits by mothers of children with symptoms, [redacted] Our findings support the general hypothesis that early lung injuries have an impact on the later respiratory health of children. (J Pediatr 1992;121:17-22)

(1), July

It has been suggested that the natural history of chronic obstructive pulmonary disease has its origins in early childhood.[1] Among the many risk factors under investigation, there is evidence for a possible role of respiratory infection in infancy,[2,3] atopy,[1] and passive smoking.[4-10] Lung injuries in early life are associated with impaired lung function,[3,5,9,11] increased prevalence of bronchial hyperresponsiveness,[3] asthma,[12] and lower respiratory tract symptoms and disease in later life.[13]

Exercise-induced bronchoconstriction is a common manifestation of childhood asthma. The pathogenesis mainly involves altered response to temperature changes in the airways with subsequent release of mediators and smooth muscle contraction.[14,15] Bronchial hyperresponsiveness as assessed by exercise tests corresponds well to clinically apparent asthma.[16] Such tests have been used in epidemiologic studies on the prevalence of childhood asthma.[17,18] We used a standardized free running test to measure BHR in a cohort of 1812 primary-school children in southern Germany and determined the risk factors for BHR.

BHR	Bronchial hyperresponsiveness
CI	95% Confidence interval
OR	Odds ratio
PEFR	Peak expiratory flow rate

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Reprint requests: T. Frischer, MD, University Children's Hospital, Freiburg/Breisgau, Mathildenstr. 1, D-7800 Germany.

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METHODS

Sampling and questionnaire. This report is based on cross-sectional data from a cohort study on childhood asthma and allergy currently being conducted in south-

western Germany. Analysis was conducted by using data from the initial survey in 1990. The study was approved by the local ethics committee of the University of Freiburg and by local school authorities. Data collection took place in three towns in the vicinity of Freiburg im Breisgau, Germany. To obtain a representative sample of the population, we invited the parents of all children entering primary school to participate. Written consent to perform the study was obtained from the parents of all participants.

Questionnaires were distributed to children in the schools, to be filled out by the parents at home. Questions concerned parental education, housing conditions, gestational age, the parents' history of allergic diseases, and the child's history of pneumonia during the first year of life. Lifetime prevalence of asthma was based either on a physician's diagnosis of asthma or on repeated diagnoses of wheezy bronchitis. Maternal and paternal smoking status during pregnancy, the child's first year of life, and the study year (1990) was recorded. For the same periods, the total number of packs of cigarettes smoked per day in the house by all family members was also recorded. Reproducibility of the responses was determined in a separate study of 162 children of the same age. The questionnaire was distributed twice to these children's parents within 4 weeks. When the first questionnaire was distributed, parents were not told about the second questionnaire.

Allergy skin test. A standardized skin-prick test using seven common allergens (birch, grass, and hazel pollen, cat and dog dander, and *Dermatophagoides pteronyssinus* and *farinae* [ALK Laboratories, Copenhagen, Denmark]) and a positive (histamine, 10 mg/ml) and a negative (sodium chloride) control test were performed on the right forearm of all children. The smallest and largest diameters of every wheal were measured after 15 minutes and the arithmetic mean was calculated. Any value equal to or greater than 2 mm was scored as positive, the value for the negative control test first being subtracted from the allergen value. Children with at least one positive reaction to any of the allergens were designated as being atopic.

Free running test. We used a standardized free running test to measure bronchial responsiveness.[15,16] Tests were performed by two observer teams, each consisting of a physician trained in pulmonary medicine, a nurse, and two students. Team members were unaware of questionnaire data and were interchanged between teams periodically. Locations varied daily. The exercise tests were performed in school gymnasiums, usually between 8 AM and 1 PM. Any antiasthma treatment was not interrupted. Children who were absent were given a second appointment. The children underwent a short physical examination, and their weight and height were recorded. Children with a cough or crackles on auscultation were classified as having recent lower respiratory tract infection. Room temperature and humidity were recorded. Each child was provided with a telemetric device to monitor heart rate. Children were exercised in groups of four for 6 minutes. With the use of the mini Wright Peak Flow Meter (Clement Clarke, Ltd., London, United Kingdom), five peak expiratory flow rate readings were recorded immediately before exercise and three readings at 3, 6, and 9 minutes, respectively, after the exercise period. The maximum value reached each time was recorded.

Statistical analysis. To assess the degree to which answers were reproducible, we calculated the proportion of agreement and the Cohen kappa statistic.[19] We defined BHR as a fall in PEFR of at least 15% from the baseline level to the value 3 minutes after exercise.[15] A logistic regression of BHR was performed. Backward elimination of potential confounders and interaction terms was carried out.[20] Explanatory variables were maternal smoking during the various time periods, prematurity, and pneumonia during the child's first year of life. A parental history of either asthma or hay fever, the child's atopic status, place of residence, indoor temperature and humidity in the gymnasium, and indexes of parental education, respiratory infections during the study year, heating and cooking, and crowding in the children's homes (in square meters per family member) were regarded as possible confounders. Because a diagnosis of asthma is preceded by the development of BHR, asthma was not specified as a predictor of BHR, but stratified analyses were performed for asthmatic status. All analyses were performed with the Statistical Analysis Systems software program (SAS Institute, Inc., Cary, N.C.).

RESULTS

Reproducibility study. Responses to the questionnaire administered on two occasions to 162 families not participating in the study showed a high degree of reproducibility. The proportion of agreement and the kappa values for maternal smoking during pregnancy, the child's first year of life, and the study year were 83%, 83%, and 87.6% (kappa: 0.51, 0.59, 0.9), respectively. Questions on asthma showed excellent agreement (proportion of agreement: 97.7%; kappa: 0.9).

Characteristics of the study population. Of the 2604 families contacted, 1812 (69.6%) participated. Of the questionnaires, 63.7% were filled out by the mother, 4.0% by the father, and 30.2% by both parents. In a sample of 347 nonresponders, the main reason for nonparticipation was the longitudinal nature of the study, involving frequent testing of the children. The mean ($\pm$ SD) age of the study population was 7.3 $\pm$ 0.4 years. A history of asthma (current or otherwise) was reported in 210 children (11.6%). Maternal smoking was common during the child's first year of life

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Table I. Prevalence of BHR (PEFR decrease ≥15% of baseline after exercise) in relation to variables of interest, stratified for asthma

	No asthma (n = 1290)		Asthma (n = 171)		Whole sample (N = 1461)	
	%	p*	%	p	%	p
Maternal smoking during pregnancy						
Yes	5.9	0.82	22.2	0.39	7.3	0.68
No	5.4		14.5		6.5	
Maternal smoking at age 1 yr						
Yes	7.3	0.13	24.2	0.13	9.0	0.06
No	4.9		13.5		6.0	
Maternal smoking at age 8 yr						
Yes	6.3	0.38	9.5	0.21	6.6	0.97
No	5.0		17.7		6.6	
Prematurity						
Yes	8.3	0.27	27.3	0.12	12.3	0.02
No	5.5		14.3		6.4	
Pneumonia during first year of life						
Yes	8.3	0.55	11.1	0.71	9.1	0.59
No	5.5		15.7		6.7	
Atopy (skin-prick test result positive)†						
Yes	10.0	0.0	31.3	0.0	14.8	0.0
No	3.7		6.2		3.9	
Parental educational level						
Low	7.1	0.18	21.3	0.42	8.5	0.12
Medium	5.4		14.6		6.7	
High	4.3		12.3		5.3	
Gender						
Male	4.8	0.3	17.4	0.54	6.5	0.72
Female	6.1		13.9		6.9	
Recent lower respiratory tract illness						
Yes	5.2	0.82	13.9	0.73	6.3	0.72
No	5.6		16.3		6.8	
TOTAL	5.5		15.8		6.7	

*Chi-square test.
†Number of children with skin-prick test and challenge test = 1363.

(22.9%) as well as in the study year (30.2%). Of mothers who had smoked during their child's first year of life, 84.9% were still smoking during the study year. On the other hand, 39.9% of mothers who had smoked during their child's first year of life had not smoked during pregnancy. During their first year of life, 5.9% of children were exposed to at least one pack per day (smoked by all family members) and 34.0% to less than one pack per day; 60.0% were unexposed. Corresponding figures were 7.7%, 33.5%, and 58.8% for exposure during the study year. Height- and gender-adjusted means for resting PEFR were 245.6 L/min in children whose mothers smoked during the child's first year of life and 249.0 L/min in children whose mothers did not. This difference was not statistically significant.

Permission to perform the free running test was refused by 226 parents, 104 children were absent, 15 children refused to participate, and 6 children were unwilling to complete the exercise. Hence data for 1461 children (81%) were analyzed. A diagnosis of asthma was as prevalent among nonparticipating children (11.3%) as in the test group (11.6%). In 98.8% of the children, heart rate increased to more than 170 beats/min—a work load sufficient to elicit bronchoconstriction in sensitive subjects.[16] A decrease in PEFR equal to or greater than 15% was recorded in 98 children (6.7%).

Association between maternal smoking and BHR. Cigarette smoke exposure at age 1 year was associated with a higher proportion of children with BHR (9.0%) than of children with smoke exposure during the study year (6.6%) (Table I). A change in maternal smoking habits seemed to influence the prevalence of BHR. Cigarette smoke exposure that occurred exclusively during the first year was associated with the highest prevalence of BHR (13.7%). Of children who continued to be exposed to cigarette smoke, 7.6% were hyperresponsive. Of children never exposed to smoke, 6.3% were hyperresponsive. The lowest proportion of children with BHR was observed in those exposed exclusively during the study year (4.4%). This relationship was more

Table II. Results of multiple logistic regression analyses, stratified for asthma *(dependent variable: BHR)*

Independent variable	No asthma		Asthma		Whole sample	
	OR	CI	OR	CI	OR	CI
Maternal smoking during pregnancy	0.81	0.3-2.19	2.20	0.29-16.57	0.90	0.39-2.07
Maternal smoking at age 1 yr	1.77	0.68-4.61	20.56	2.5-168.9	2.82	1.26-6.35
Maternal smoking at age 8 yr	0.77	0.34-1.74	0.05	0.005-0.61	0.46	0.22-0.98
Prematurity	1.75	0.71-4.32	1.56	0.41-5.95	2.09	1.05-4.16
Pneumonia during first year of life	2.28	0.5-10.48	0.92	0.08-10.12	1.71	0.48-6.12
Atopy (skin-prick test result positive)	2.68	1.5-4.78	10.37	2.93-36.64	4.11	2.55-6.61
High educational level	0.42	0.21-0.82	0.39	0.1-1.55	0.43	0.24-0.77
Female gender	1.41	0.80-2.46	1.44	0.49-4.24	1.34	0.83-2.15

pronounced among those with asthma. Of eight children with asthma who had a history of smoke exposure exclusively during their first year of life, four were hyperresponsive. In contrast, none of the children with asthma who were exposed only during the study year (n = 16) had BHR.

To investigate whether the observed association between early exposure to cigarette smoke and BHR could be expressed as a dose-dependent relationship, we calculated the prevalence of BHR for different categories of exposure as assessed by the daily number of packs of cigarettes smoked in the household. For exposure during the child's first year, the prevalence of BHR increased from 6.5% when smoking was denied, to 6.8% when less than one pack was smoked, and to 9.6% when at least one pack was smoked. For subjects with asthma, corresponding figures were 14.8%, 17%, and 25%, respectively. A similar pattern was not found for the relationship between daily packs of cigarettes smoked during the study year and BHR.

Multivariate analysis. Results of the logistic regression analyses are shown in Table II. Smoke exposure at age 1 year was a significant predictor of BHR (odds ratio: 2.82; 95% confidence interval: 1.25 to 6.34), whereas current maternal smoking was negatively associated with BHR (OR: 0.46; CI: 0.22 to 0.97). No association between maternal smoking during pregnancy and BHR could be demonstrated. When paternal smoking during the child's first year of life and study year was added to the final model, no significant association with BHR was found. Parameter estimates for maternal smoking remained virtually unchanged.

When the analyses were repeated for subjects with and those without asthma separately, smoke exposure at age 1 year was the predominant predictor for BHR (OR: 20.56; CI: 2.5 to 168.9) in the asthmatic group; current smoking was negatively associated with BHR (OR: 0.05; CI: 0.005 to 0.61). In children without asthma, the OR for current smoke exposure was still less than 1 (OR: 0.77; CI: 0.34 to 1.74) and more than 1 for smoke exposure during the first year (OR: 1.77; CI: 0.67 to 4.61).

DISCUSSION

The results of many studies convincingly support the hypothesis that passive smoking leads to a decrease in lung function and possibly to delayed lung growth in young children.[4-10] The relationship of smoke exposure to bronchial responsiveness, atopy, and the development of asthma is less evident, and findings have been inconsistent.[10] Although some population-based studies have established a positive relationship between smoke exposure and persistent wheeze,[21] bronchial hyperresponsiveness,[22, 23] or asthma,[12] others have not.[7, 24, 25]

To our knowledge, there are no studies that have examined the role of active smoking in the development of BHR in young children. Data on active smoking by 7-year-old children in Germany are not available, but we believe that it is unlikely that active smoking could have influenced our findings.

[redacted][22, 26, 27] In this analysis, no effect of cigarette smoke exposure during pregnancy could be found. Of 258 mothers who smoked during pregnancy, only 20 (7.8%) discontinued smoking after delivery, whereas 158 (39.9%) of 396 mothers who smoked during the child's first year of life had not smoked during pregnancy. Hence our study might have lacked the power to measure an independent effect of maternal smoking during pregnancy. Recently Young et al.[23] demonstrated increased bronchial responsiveness to histamine in a group of 13 infants aged 4½ weeks when parental smoking during pregnancy was reported. It has been suggested that interference with the immune system is one underlying mechanism.[27] Martinez et al.[22] observed an increase in atopy in boys exposed to parental smoking. Our findings concerning the relationship between smoke exposure and BHR cannot be explained by an increase in atopy among children exposed to smoke, because atopy was an independent predictor of BHR in the regression analyses.

Theoretically smoke exposure throughout a child's life (first year and study year) should be most harmful. In this

report. [redacted] current exposure was negatively associated with BHR; [redacted] The same risk applied to children exposed only during the first year compared with children never exposed.

The relationship between smoke exposure and BHR was significant only in those with asthma. The power of finding a significant relationship for those without asthma might have been too small, however, because the proportion of responsive subjects without asthma was low (5.5%).

One possible explanation for the negative association between smoking during the study year and BHR in children with asthma could be a tendency of mothers to quit smoking when the child had respiratory symptoms [redacted] because BHR, as assessed by exercise challenge, is thought to reflect the severity of disease in children with asthma.[18] Although smoke exposure during the child's first year of life was as common among subjects with as among those without asthma, more mothers quit smoking between their children's first birthday and the study year when asthma was diagnosed. It is also possible that 7-year-old children might be less susceptible[28] to lung injuries and might spend less time with their parents. Furthermore, the challenge we used might not have been sensitive enough to detect subtle changes in responsiveness. Martinez et al.[22] measured bronchial responsiveness by means of a carbachol challenge test in 9-year-old schoolchildren; current parental smoking was associated with increased responsiveness. However, the observed relationship between current smoke exposure and BHR could have been due to exposure at an early age, because 7 of 10 children whose mothers smoked regularly throughout pregnancy were hyperresponsive. Similar findings to those presented here were reported by O'Connor et al.,[24] who challenged children aged 10 to 12 years by means of eucapnic hyperventilation with subfreezing air; maternal smoking was related to BHR in children with but not in those without asthma. They suggested that passive smoking could interfere with growth of the lungs of children with asthma; the history of smoke exposure was not analyzed, and hence exposure at an early age might have been responsible for the observed association. Strachan et al.[7] performed exercise challenge tests in 7-year-old children in Great Britain; current smoke exposure was determined by saliva cotinine analysis. As in our report, current exposure was not related to BHR; exposure to tobacco smoke earlier in life was not investigated.

This study presents evidence supporting the link between smoke exposure in early life and the presence of BHR in primary-school children, particularly in those with a diagnosis of asthma or recurrent wheezy bronchitis. In studying the effects of current passive smoking in children, prior exposure to tobacco smoke must be taken into consideration.

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Cross-sectional data of a longitudinal study in Southwest Germany were used by the authors of this study to evaluate early childhood risk factors for current sensitization in 1470 children aged 6-8 years. The authors reported odds ratios for unilateral parental atopy (1.9), bilateral parental atopy (2.8), low gestational age (1.9), and male gender (1.6). The authors reported that "breast feeding, maternal smoking habits after the child's birth, prior exposure to pets, and social class are not important."

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Early childhood risk factors for sensitization at school age

Joachim Kuehr, MD,[a] Thomas Frischer, MD,[a] Wilfried Karmaus, MD, MPH,[b] Rolf Meinert, MSc,[a] Regina Barth, MD,[a] Edelgard Herrman-Kunz, MD,[a] Johannes Forster, MD,[a] and Radvan Urbanek, MD[c]

Freiburg and Hamburg, Germany, and Vienna, Austria

Early childhood risk factors for current sensitization were investigated by use of cross-sectional data of a longitudinal study in Southwest Germany. Information was gathered by questionnaires from 1812 families of whom 1470 children 6 to 8 years old were tested by means of a skin prick test (SPT) with seven aeroallergens. Groups with sensitization (n = 201: positive SPT to grass pollens 6.6%, Dermatophagoides pteronyssinus 6.5%, Dermatophagoides farinae 4.4%, cat dander 4.6%, any of the tested allergens 13.7%) are compared with children without sensitization (n = 1269). As risk factors for any sensitization parental atopy (odds ratio [OR]/95% confidence interval [95%CI]: unilateral 1.9/1.3 to 2.6; bilateral 2.8/1.5 to 5.2), low gestational age (1.9/1.1 to 3.2), and male gender (1.6/1.2 to 2.3) are statistically significant in multiple logistic regression. Former cat ownership is significantly related to sensitization to cat dander (2.7/1.4 to 5.5). Breast-feeding, maternal smoking habits after the child's birth, prior exposure to pets, and social class are not important. In conclusion, our data suggest parental atopy, low gestational age, and male gender as independent risk factors for sensitization to aeroallergens at school age. (J ALLERGY CLIN IMMUNOL 1992;90:358-63.)

Key words: Childhood, risk, sensitization, familial, smoking, gender

In childhood, sensitization to aeroallergens is a major cause for chronic respiratory diseases such as hay fever and bronchial asthma.[1-3] Numerous epidemiologic and clinical studies were carried out to analyze the pathogenesis of atopic diseases.[4-14] Sensitization to allergens is usually estimated by use of skin prick tests (SPT) or by measurement of allergen-specific IgE antibodies.[4-7, 9, 10, 13, 14] Some studies have demonstrated that risk factors for atopy (i.e., allergen exposure) may act antigen specific.[5, 6, 13-16] Parental atopy (PA) and early exposure to potent allergens like cow's milk proteins or pollens are risk factors for sensitization in later life.[4, 6, 11-13, 16-19] Presumable risk factors for sensitization are social class,[20-22] gender,[10, 23-25] early respiratory infections,[5, 7, 26, 27] and tobacco smoke exposure.[8, 12, 14, 28, 29]

Abbreviations used	
SPT:	Skin prick test
PA:	Parental atopy
LGA:	Low gestational age
MSP:	Maternal smoking during pregnancy
Dpt:	*Dermatophagoides pteronyssinus*
Df:	*Dermatophagoides farinae*
OR:	Odds ratio
95% CI:	95% confidence interval
HDM:	House dust mite

We analyzed data derived from a cross-sectional investigation of an ongoing longitudinal study in Southwest Germany comprising 1812 schoolchildren to test these risk factors in regard to sensitization in SPT. In addition, we investigated low gestational age (LGA) and potential combined effects on current sensitization to aeroallergens.

POPULATION IN THE STUDY AND METHODS

The data were collected in a first cross section of a longitudinal study designed to assess risk factors for allergy

From the University Children's Hospital, Freiburg,[a] NORDIG Institute for Health Research and Prevention, Hamburg,[b] and University Children's Hospital, Vienna.[c]

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Reprint requests: Joachim Kuehr, MD, University Children's Hospital, Mathildenstr. 1, W-7800 Freiburg, Germany.

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and asthma in children. To obtain a population-based sample of schoolchildren between 6 and 8 years of age, all parents whose children had started elementary school were invited to participate. Questionnaires were distributed to 2604 families living in three urban areas in Southwest Germany (Freiburg, Kehl, and Lörrach) from February to April 1990. The questionnaires were returned by 1812 families (participation: 70%). In 94% the questions were answered by the mothers. Appended to the questionnaire was a written consent for the children to participate in further investigations (SPT and free running test). The SPT took place from March to June in the same year. A population of 1470 children participated in the SPT. The study was approved by the local ethical committee and also by local school authorities.

Questionnaire

Thirty to 45 minutes were used to fill in answers. The reproducibility of the answers was determined in a separate study with 162 primary school children. Questionnaires were administered by the parents on two occasions 14 days apart from each other. In the following the proportion of agreement (%) is given in brackets. For the analyses, questions of interest are the following: parental atopy (PA, maternal or paternal history of asthma or hay fever or eczema; 94%); low gestational age (LGA, child born at least 3 weeks preterm); maternal history of cigarette smoking during pregnancy (MSP, 80%), in the first year of the child's life (81%), and in the year preceding the cross-sectional investigation (85%); duration of breast feeding (in months); history of pneumonia and history of whooping cough in the child's first year of life (94% and 87%); history of an exposure to pet animals at home (previous exposure and current exposure); social class (highest educational level achieved at school by father or mother; 87%); gender of the child.

SPT procedure

Seven purified and immunochemically characterized aeroallergens (Allergologisk Laboratorium, A/S, Copenhagen, Denmark) were applied to the child's forearm with the aid of an uncoated Phazet needle (Pharmacia Diagnostics, AB, Uppsala, Sweden). The reactions were recorded after 15 minutes.[30] Extracts from grass pollens (mixture of the six most common species), birch and hazel pollens, *Dermatophagoides pteronyssinus (Dpt)* and *Dermatophagoides farinae (Df)* as well as cat and dog dander were used (concentration: 10 histamine equivalent in prick testing). As control solutions, histamine hydrochloride (10 mg/ml) and sodium chloride (9 gm/L) were applied. The largest and the orthogonal diameter of a wheal were measured by means of a transparent ruler, and the arithmetic mean was calculated. A reaction to the negative control was subtracted from the allergen value. A wheal of 3 mm or more was classified as a positive reaction. The tests were carried out by two nurses under supervision of a physician.

Statistical analysis

The questionnaire data were categorized, and differences between the groups with and without reaction in SPT were examined by chi-square tests. The estimation of the relative risks was based on logistic regressions and provided odds ratios (ORs) and their 95% confidence intervals (95% CI).[31, 32] In the assessment we followed the backward procedure by Greenberg et al.[33] that starts with a model including all potential confounders. Reducing the model backward, the potential confounder social class could be eliminated if no change in the parameter estimates of the variables of interest occurred (≤10% in change). In addition, to investigate an effect of parental atopy together with MSP, gender, and LGA, ORs for the different combinations of these variables were calculated.[34] The expected ORs (OR_{exp}) for a combination of two factors were derived from observed ORs (OR_{obs}) as follows: $OR_{exp11} = OR_{obs10} + OR_{obs01} - 1$.[34] The formula is based on an additive model with no interaction.

RESULTS

A sensitization to any of the seven tested allergens is found in 13.7% of the 1470 children, of whom 6.6% are sensitized to grass pollens, 6.5% to *Dpt*, 4.4% to *Df*, and 4.6% to cat dander (Table I). In 109 children (7.4% of 1470) an SPT reaction occurs to at least one of the two house dust mites (HDMs) (46% to both, 41% to only *Dpt* and 13% to only *Df*).

Bivariate analyses

It is evident from Table I that unilateral PA (one atopic parent) is more frequent in children sensitized to any of the seven or to one of the single allergens tested, respectively. This is also true for the bilateral parental affection. Maternal atopy was reported in 21% compared with a paternal history in 18%. A gestational age of 37 weeks or less (LGA) is found in 7% of the nonatopic children and has a significantly higher prevalence in three of the sensitized subgroups (Table I). MSP is most frequent in the subgroup with no sensitization and is less frequent in children with sensitization to any allergen, *Df*, and cat dander. Former cat ownership is associated with a higher prevalence of sensitization to cat dander. In each of the sensitized subgroups more boys than girls are found. A history of pneumonia in the child's first year of life is rare and is reported significantly more frequently only in the group sensitized to cat dander.

Multivariate analyses

The potential effects of the variables of interest (listed in Table I) on the SPT sensitization were estimated by multiple logistic regression (Table II). The models were based each on the comparison of the sensitized subgroup ('any,' grass pollens, *Dpt*, *Df*, cat dander) with the nonsensitized population ($n = 1122$; missing data excluded). The ORs derived from the five regression models indicate a 1.6-fold to 2.5-fold risk of unilateral and a 1.5-fold to 3.1-fold risk of bilateral PA for sensitization. LGA is significantly related to sensitization to *Df* and *Dpt* as well as to any

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TABLE I. Percentages of risk factors for different SPT results

Factor	Sensitization to None (n = 1269)	Any (n = 201)	Grass (n = 97)	Dpt (n = 95)	Df (n = 64)	Cat (n = 67)
Parental atopy						
None	67.3	51.2***	52.6***	50.5**	50.0**	46.3***
Unilateral	28.5	39.3	36.1	41.1	39.1	49.3
Bilateral	4.2	9.5	11.3	8.4	10.9	4.5
Low gestational age	7.0	11.6*	7.2	18.1***	18.8***	12.1
Breast feeding						
<8 months	18.5	22.5	19.6	28.7	20.3	20.9
≤4 months <8	18.5	21.0	18.6	18.1	29.7	26.9
≤1 months <4	37.0	31.5	33.0	29.8	32.8	28.4
month <1	25.9	25.0	28.9	23.4	17.2	23.9
Maternal smoking						
Pregnancy	15.8	9.1*	8.6	10.6	3.2**	6.1*
First year of life	23.5	18.1	17.9	20.2	15.9	16.7
Previous year	30.7	25.0	26.3	26.1	25.4	22.7
Whooping cough in the first year	6.0	5.6	6.4	4.4	3.3	7.7
Prior exposure to cat dander	9.6	11.0	9.3	7.4	7.8	19.4**
Current exposure to cat dander	16.6	10.5*	13.4	10.5	9.4	19.4
Prior exposure to pets	27.8	31.3	28.9	26.3	29.7	40.3*
Current exposure to pets	44.4	42.8	46.4	44.2	39.1	50.8
Social class						
Low	34.4	29.6	28.0	33.3	26.6	27.3
Medium	28.0	30.6	33.3	32.3	28.1	39.4
High	37.7	39.8	38.7	34.4	45.3	33.3
Gender (male)	46.8	60.2***	53.6	66.3***	64.1**	56.7
Pneumonia in the first year	2.4	4.0	2.1	5.3	3.1	9.0***

Percentages based on numbers after "missings" have been deleted.
Significance in chi-square test (*$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$) for the atopic groups compared with the group with no sensitization.

TABLE II. Odds ratios/95% confidence intervals of risk factors for atopy with mutual adjustment

Factor	Sensitization to Any of 7 antigens	Grass pollens	Dpt	Df	Cat dander
Parental atopy					
Unilateral	1.87/1.32 - 2.63	1.64/1.02 - 2.64	2.23/1.37 - 3.62	1.70/0.95 - 3.04	2.50/1.44 - 4.33
Bilateral	2.79/1.51 - 5.18	3.13/1.42 - 6.92	2.76/1.16 - 6.55	2.98/1.17 - 7.55	1.52/0.43 - 5.42
Low gestational age	1.92/1.15 - 3.21	1.06/0.46 - 2.42	3.57/1.93 - 6.61	3.61/1.75 - 7.43	2.40/1.05 - 5.49
Maternal smoking in pregnancy	0.57/0.28 - 1.14	0.39/0.15 - 1.02	0.81/0.31 - 2.08	0.17/0.03 - 0.82	0.31/0.09 - 1.07
Prior exposure to cat dander	—	—	—	—	2.75/1.37 - 5.52
Gender male	1.64/1.19 - 2.26	1.21/0.78 - 1.89	2.12/1.33 - 3.39	2.20/1.26 - 3.84	1.68/0.99 - 2.86

Outcome variables: sensitization in SPT to 'any' allergen (n = 182), grass pollen (n = 87), *Dpt* (n = 86), *df* (n = 60), cat dander (n = 62), each in relation to no sensitization (n = 1122).

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allergen, with minor risk for the latter. With the exception of sensitization to *Df*, no significant relationship can be shown between SPT results and maternal smoking habits. In case of sensitization to *Df* MSP is less frequent than in the group with no reaction (OR, 0.17). In the children sensitized to cat dander former cat ownership is of significance for a current sensitization (OR, 2.75). Male gender is a significant risk for sensitization to both HDMs (*Dpt* and *Df*) and to any of the tested allergens.

Combined effects

As shown in Table II PA is a general predictor for sensitization in SPT. To investigate combined effects in which PA as one predictor might be involved, we analyzed combined effects with MSP, gender, and LGA, respectively, on SPT. For PA with gender and LGA no interaction could be seen (not shown). For MSP alone, a decreased risk of MSP in the absence of PA is found (ORs, 0.5 to 0.6; Table III). To consider different patterns of the mother's or father's atopic history and MSP, PA was additionally stratified for exclusive maternal or paternal history (bilateral parental atopy excluded). The ORs for maternal and paternal atopy indicate increased risks of both parental histories. A uniform combined effect of maternal and paternal atopy, respectively, together with MSP cannot be seen (ORs, 0.6 to 1.4). However, each of the observed ORs for the combinations are below the expected values. This pattern is not of significance, because the confidence intervals of the observed ORs include the expected values.

DISCUSSION

In the present epidemiologic study, PA, LGA, and male gender were identified as risk factors for allergic sensitization at school age.

To our knowledge, no previous results regarding the relationship between LGA and atopy in school-aged children are available. However, on the basis of the immune response of fetal and newborn mice, immunologic and digestive immaturity have been postulated to prevent tolerance in the case of an antigen feed in the neonatal period.[35] A high risk of early exposure to cows' milk for developing allergic reactions in early infancy has been shown in preterm babies with an additional family history of atopy.[36] This may be one potential explanation for the association of LGA with sensitization to common aeroallergens. However, the issue is still in dispute, whether such individuals with milk protein allergy have a higher likelihood of developing inhalative allergies later in life than do children without previous sensitization to food allergens. A sequence of this type is known in principle from the natural course of atopic diseases.[9] On the basis of our data we were not able to elucidate the sequence of these early events.

The role of gender in atopic diseases has repeatedly been reported. Several authors confirm our findings, which indicate that males have a stronger predisposition for sensitization than females.[10, 23, 24] However, a recently published large study did not find a relationship.[25] One explanation for a gender predominance may be the so-called Carter effect, assuming different thresholds of polygenic inheritance.[37] In addition to allergy related data, this hypothesis is supported by the predominance of males with bronchial asthma at school age.[38, 39] Male predominance in HDM allergy as well as bronchial asthma might be related to each other, considering that HDM allergens are regarded as the most important trigger of perennial allergic asthma in childhood.[40] Male gender and LGA have in common that an association with sensitization can be observed to occur most often in positive SPT to both types of HDM and less often with respect to at least one allergen (any) but not to cat dander and grass pollen (Table II). Therefore it can be assumed, that these risks may exist not only for atopy in general, but, as is the case here, for a specific phenotype.

Most authors have reported an effect of atopic family history that is comparable with our results.[12, 13, 18, 41] For children without genetic disposition, the prevalence of atopy varied between 12% and 27% compared with 10.8% in our population.[12, 41] In case of a positive family history the prevalences ranged between 23% and 43% compared with 19.1% in the current study.[12, 41] Findings vary according to country, study population, and instruments used. The results concerning the genetic effect on the offspring also appears to depend on the prevalence of atopy at each respective age. The effect of PA is estimated higher in children reaching school age than for infancy.[11-13, 18, 41, 42]

A differentiation of parental histories shows increased ORs for maternal (ORs, 1.5 to 2.3) as well as paternal atopy (ORs, 1.9 to 2.9) if the mother did not smoke during pregnancy (Table III). We did not expect that MSP as a single predictor would be associated with a lower frequency of sensitizations (ORs, 0.5 to 0.6). Hence, the combined risks of MSP and maternal (ORs, 0.7 to 1.4) as well as paternal atopy (ORs, 0.4 to 1.0) are not significant for sensitization. Although not significant, the observed negative association of MSP and sensitization in SPT was surprising to us.

An effect of MSP on fetal Ig regulation has been shown. In cord blood significantly higher levels of IgA, IgG, as well as IgM were found in the offspring

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TABLE III. Frequencies, OR, and 95% CI for combinations of PA with MSP

		Sensitization to								
		Any			Grass			Dpt		
Factor 1	Factor 2	Yes	No	OR/95% CI	Yes	No	OR/95% CI	Yes	No	OR/95% CI
PA −	MSP −	90	688	1	43	688	1	42	688	1
PA −	MSP +	10	139	0.5/0.3 - 1.1	5	139	0.6/0.2 - 1.5	5	139	0.6/0.2 - 1.5
Maternal +	MSP −	39	168	1.8/1.2 - 2.7	16	168	1.5/0.8 - 2.8	18	168	1.8/1.0 - 3.1
Maternal +	MSP +	3	24	1.0/0.3 - 3.2 (1.3)†	1	24	0.7/0.1 - 5.0 (1.1)	2	24	1.4/0.3 - 6.0 (1.4)†
Paternal +	MSP −	34	134	1.9/1.3 - 3.0	17	134	2.0/1.1 - 3.7	18	134	2.2/1.2 - 3.9
Paternal +	MSP +	2	25	0.6/0.1 - 2.6 (1.4)†	1*	25	0.6/0.1 - 4.8 (1.6)	1	25	0.7/0.1 - 5.0 (1.8)†

*To estimate the odds-ratio one artificial case was added to an empty cell, which gives conservative estimates.
†The values in brackets are the expected ORs for the combination of MSP with maternal and paternal atopy, respectively.

on 163 women who smoked, as compared with 130 women without a history of smoking.[43] After an 18-month follow-up, a significantly higher cord blood IgE in the case of maternal smoking was reported.[44] Smoking behavior, however, was established for the age of 18 months, but not for the pregnancy.[8] An effect of MSP on the cord blood IgE concentration could not be shown in a population of 136 newborn children, 16 of whose mothers had smoked during pregnancy.[45]

On the basis of the literature, (an) immunologic effect(s) of passive smoke exposure seem(s) likely. Nevertheless, a potential role of MSP in the atopic history of the offspring is still not sufficiently understood. Thus we do not interpret our results to show an independent effect of MSP on atopy in the offspring.

In regard to our findings we must point out that the retrospective ascertainment, which encompasses a period of time spanning 8 years, can be limiting for the reliability of risk assessment. Since the risk of LGA can have implications for the care of newborns, we examined the child's birth record in a representative sample of the population (n = 287). In 96%, consistency of questionnaire and birth record is found, and for 73% of children classified to LGA, accuracy of recall is demonstrated. The present analyses did not identify statistically significant relationships between breast feeding, postpartal maternal smoking, whooping cough in the first year of life, and educational status on one hand and sensitization in SPT on the other.

In conclusion, our data show that parental atopy represents a general risk for sensitization at school age. A higher risk of sensitization is seen in children with bilateral parental atopy, than in the case of unilateral parental atopy. Among the other variables of interest, LGA and male gender point to a significant relationship primarily to sensitization to HDM allergens. Furthermore, the observed significance of prior, but not of present, cat ownership in relationship to current sensitization provides one example that a recognition of changed patterns of behavior is necessary for retrospective ascertainments in epidemiologic studies.

We thank Mrs. Monika Mortensen and Mrs. Sabine Linser-Haar for their excellent collaboration in the field study conducting the SPT.

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Sensitization to		
Cat		
Yes	No	OR/95% CI
28	688	1
3	139	0.5/0.2 - 1.8
16	168	2.3/1.2 - 4.4
1*	24	1.0/0.1 - 7.8 (1.8)†
16	134	2.9/1.5 - 5.6
1*	25	1.0/0.1 - 7.5 (2.4)†

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Arshad, S.H., Matthews, S., Gant, C., and Hide, D.W., "Effect of Allergen Avoidance on Development of Allergic Disorders in Infancy," <u>The Lancet</u> 339: 1493-1497, 1992.

In this study of 120 infants with a family history of atopy and high cord-blood concentrations of total IgE, the authors reported that parental smoking was a significant risk factor for total allergy at 12 months. The reported odds ratio was 3.97 (95% CI: 1.2-13.6) when one parent smoked and 4.72 (95% CI: 1.2-18.2) when both parents smoked. The authors suggested that "passive smoking is an important risk factor that should be addressed in any prophylactic programme."

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ORIGINAL ARTICLES

Effect of allergen avoidance on development of allergic disorders in infancy

SYED H. ARSHAD SHARON MATTHEWS CAROLE GANT
DAVID W. HIDE

There is much evidence that the development of allergic disorders may be related to early exposure of allergens, including those in breastmilk. We have tried to find out whether avoidance of food and inhaled allergens in infancy protects against the development of allergic disorders in high-risk infants.

In a prenatally randomised, controlled study 120 infants with family history of atopy and high (>0·5 kU/l) cord-blood concentrations of total IgE were allocated randomly to prophylactic and control groups. In the prophylactic group (n = 58), lactating mothers avoided allergenic foods (milk, egg, fish, and nuts) and avoided feeding their infants these foods and soya, wheat, and orange up to the age of 12 months; the infants' bedrooms and living rooms were treated with an acaricidal powder and foam every 3 months, and concentrations of *Dermatophagoides pteronyssinus* antigen (*Der p* I) in dust samples were measured by enzyme-linked immunosorbent assay. In the control group (n = 62), the diet of mothers and infants was unrestricted; no acaricidal treatment was done and *Der p* I concentrations were measured at birth and at 9 months. A paediatric allergy specialist unaware of group assignment examined the infants for allergic disorders at 10–12 months. Odds ratios were calculated by logistic regression analysis for various factors with control for other confounding variables. At 12 months, allergic disorders had developed in 25 (40%) control infants and in 8 (13%) of the prophylactic group (odds ratio 6·34, 95% confidence intervals 2·0–20·1). The prevalences at 12 months of asthma (4·13, 1·1–15·5) and eczema (3·6, 1·0–12·5) were also significantly greater in the control group. Parental smoking was a significant risk factor for total allergy at 12 months whether only one parent smoked (3·97, 1·2–13·6) or both parents smoked (4·72, 1·2–18·2).

Reduced exposure of infants to allergens in food and in housedust lowered the frequency of allergic disorders in the first years of life. [redacted]

Lancet 1992; 339: 1493–97.

Introduction

In infancy, a family history of atopy is the most important predictor of risk of allergic disorders such as allergic asthma and atopic eczema. A high cord-blood concentration of IgE may also be useful in predicting atopy.[1] There is evidence that immediate hypersensitivity in later life depends on allergenic factors encountered in infancy.[2-5] Sporik and colleagues' study[6] suggests that the development of sensitivity to housedust-mite antigen and the symptoms and severity of asthma in later childhood are directly related to exposure to the antigen in infancy, and infants exposed to cats from birth show increased sensitisation to cat dander.[7] Parental smoking and household overcrowding may be contributing factors.[8,9] Among infants who first receive egg yolk at the age of 3 months intolerance of this food is common, whereas intolerance is rare when egg yolk is introduced at 9 months or later.[10] In 1936, Grulee and Sanford[11] showed a seven-fold increase in eczema in babies fed cows' milk. However, the subject remains controversial.[12]

Small amounts of protein ingested by the mother are secreted unchanged into breastmilk.[13,14] In this way potentially allergenic food eaten by the mother can be transferred to the infant and can cause sensitisation. Thus, maternal dietary restriction during lactation seems to be important.[15-17] We have tried to find out whether avoidance of food and housedust-mite allergens in early life protects against the development of allergic disorders in at-risk infants.

ADDRESS: Clinical Allergy Research Unit, St Mary's Hospital, Newport, Isle of Wight PO30 5TG, UK (S. H. Arshad, MRCP, S Matthews, SRN, C. Gant, SRD, D. W. Hide, FRCP). Correspondence to Dr David W. Hide.

Subjects and methods

This was a prospective, prenatally randomised, controlled study; assessment was done by observers unaware of group allocation. The prenatal inclusion criteria were dual heredity (allergic disease in both parents, one parent and one sibling, or two siblings) or single heredity (allergic disease in one parent or sibling); for the latter infants cord-blood IgE had to be high (>0·5 kU/l). Between March, 1990, and February, 1991, a research nurse explained the study to all pregnant women (1116) in one district hospital at their last antenatal visit. 504 (45%) reported a history of allergic disease (previously diagnosed asthma, atopic eczema, allergic rhinitis, or food allergy) in themselves, their partners, or their children. 301 (60%) agreed to take part in the study and gave informed consent. 143 mothers were randomly allocated to the prophylactic group, which was instructed about avoiding allergens, and 158 to the control group, based on a computer-generated list of random numbers. Odd numbers were assigned to the control group and even numbers to the prophylactic group.

Total IgE was measured by enzyme-linked immunoassay (Ultra, Pharmacia, Uppsala, Sweden), which can detect 0·2 kU/l to 50 kU/l. The IgE result was available within a few days of birth. The diet of mothers and infants in the prophylactic group was restricted until that time. 162 of the 194 infants with single heredity (prophylactic 72, control 90) were excluded since their cord-blood IgE was less than the entry requirement. 3 premature infants (prophylactic 2, control 1) were also excluded because of their special dietary requirements. Of 301 women randomised before birth, the infants of 136 met the inclusion criteria and entered the study.

16 infants did not complete follow-up (prophylactic 11, control 5). 1 infant in the prophylactic group was given cows' milk formula in the nursery by mistake and 10 mothers found the diet too restrictive and gave up within the first 4 weeks (in most within the first few days). These infants were not followed up. In the control group, 3 mothers did not attend the follow-up clinic and 2 left the area.

In the prophylactic group, lactating mothers followed a strict dietary regimen that excluded dairy products, egg, fish, and nuts. Up to 9 months breastfeeds were supplemented, if necessary, with a soya-based protein hydrolysate (Aptamil HA, Milupa, UK). Formula-fed infants received Aptamil HA from birth. The infants' diet was free of dairy products, egg, wheat, soya (unhydrolysed), orange, fish, and nuts. Cows' milk and soya were introduced at 9 months, wheat at 10 months, and egg at 11 months. After 12 months there was no restriction on the infants' diet. A dietitian explained the dietary restrictions in detail to all mothers when their infants were born. Written instructions were also provided with a list of foods to take and to avoid at various stages for both mother and infant. All lactating mothers were provided with calcium (1000 mg/day) and vitamin supplements.

The prophylactic group also avoided housedust-mite antigen. All infants used polyvinyl-covered mattresses with vented head area. The infants' homes were visited during the first week of life. In each home, nurses collected dust samples, by means of a hand-held mains-operated (500 W) vacuum cleaner (Hoover, UK) with dust filters (ALK, Denmark), from the infants' bedroom carpet, the living-room carpet, and upholstered furniture. No significant amounts of dust were obtained from covered mattresses. Antidust-mite treatment with Acarosan (Crawford Chemicals, UK) foam and powder was applied to the infant's bedroom carpet, living-room carpet, and upholstered furniture. This procedure was repeated every 3 months to 9 months. Dust samples were analysed by a sandwich-type enzyme-linked immunosorbent assay with monoclonal-antibody-labelled discs (ALK, Denmark) for the main antigen of *Dermatophagoides pteronyssinus* (*Der p* I).

Mothers and infants in the control group followed a normal diet advised by their health-visitors. The homes of control-group infants were visited soon after delivery and at 9 months of age for collection of dust samples for *Der p* I measurement.

All infants and mothers attended hospital clinics at 3 and 6 months. Any symptoms and signs related to allergic disorder were recorded and appropriate advice was given. Further visits were arranged if necessary for assessment of any allergy-related disorders. A dietitian assessed the nutritional adequacy of the diet for infants and mothers in the prophylactic group. Compliance with the prophylactic regimen was checked by questioning of the mother, regular home visits by research nurses, and analysis of breastmilk samples for cows' milk protein (bovine casein and lactoglobulin). Between 4 and 12 weeks, 8 mothers gave up the diet. 3 infants were introduced to cows' milk and wheat between 24 and 32 weeks. These infants were included in the final analysis.

At 10–12 months, a paediatric allergy specialist unaware of group allocation examined all children for allergic disorders. Asthma was defined as three or more separate episodes of cough and wheezing and eczema as chronic or chronically relapsing dermatitis (lasting more than 6 weeks) with characteristic morphology (areas of scaly, erythematous, pruritic lesions) and distribution (face, postauricular area, scalp, extensor surface of arms and legs, and flexural creases). Food intolerance was defined as a history of vomiting, diarrhoea, colic, or rash within 4 h of ingestion of a recognised food allergen. The food was excluded from the diet for 4 weeks and a diagnosis of food intolerance was accepted if symptoms recurred on open challenge. All skinprick tests were done by one research nurse with allergen extracts (Soluprick ALK, Denmark) against housedust mite, grass pollen, cat dander, cows' milk, egg, and any other allergen implicated in a particular case. A mean wheal diameter (half the sum of largest diameter and its perpendicular) of more than 2 mm but at least half the size of the wheal produced with histamine was regarded as positive.

Information on the presence of pets and parental smoking habits was obtained at the prenatal visit and updated at each visit. Parents were regarded as smokers if they regularly smoked one or more

TABLE I—CHARACTERISTICS OF STUDY GROUPS

—	Prophylactic (n = 58)	Control (n = 62)
No included with		
Dual heredity	51	42
Single heredity plus high IgE	7	20
No with allergy in		
Mother	42	41
Father	31	34
Sibling	36	31
Mean cord-blood IgE (kU/l)		
25th percentile	0·34	0·49
50th percentile	0·65	0·66
75th percentile	0·85	0·81
90th percentile	0·95	0·93
Male/female	28/30	34/28
No with smoking by		
Mother	8	16
Father	21	22
Either	21	27
No in socioeconomic group		
High (A, B, C)	30	33
Low (D, E)	28	29
No sharing bedroom	26	25
No with pets in household	36	38

TABLE II—INFANT FEEDING PRACTICES

—	% of group	
	Prophylactic	Control
Breastfeeding		
From birth	71	77
At 3 mo	43	48
At 6 mo	28	31
At 9 mo	17	15
*Formula feeding**		
1 mo	50	44
3 mo	78	71
6 mo	88	84
Solid foods		
3 mo	40	48
6 mo	97	97

*Aptamil HA in prophylactic group and cows' milk formula in controls.

cigarettes a day. Birthweight was recorded and infants were weighed at each visit. Information was also obtained on social class (classified by father's occupation except when the mother was single or the father unemployed and the mother employed) and whether the infant shared a bedroom with parents or other children. The social classes were defined according to the Registrar-General's classification. Analysis was done with classes 1, 2, and 3 grouped together as the higher socioeconomic group and classes 4 and 5 as the lower socioeconomic group.

We sought a 50% reduction in allergic disorder in the prophylactic group. This large reduction combined with the likely high incidence of allergy in this population meant that at least 60 infants were required in each group to give 80% power of detecting a difference at 5% significance. For *Der p* I, comparison of group means was done by the unpaired *t* test and means within groups were compared by the paired *t* test. Logistic regression analysis was used to assess the independent contribution of factors to the risk of allergic disorders. The presence of any allergic disorder at 3, 6, and 12 months' follow-up and individual allergic disorders at 12 months was used as the dependent variable. All risk factors of interest were included in the model and significance was tested for each one, with control for all other factors, by means of the Wald statistics. Adjusted odds ratios with 95% confidence intervals (CI) were calculated. Statistical analysis was done with SPSS/PC+ V4 (SPSS, Chicago, Illinois, USA).

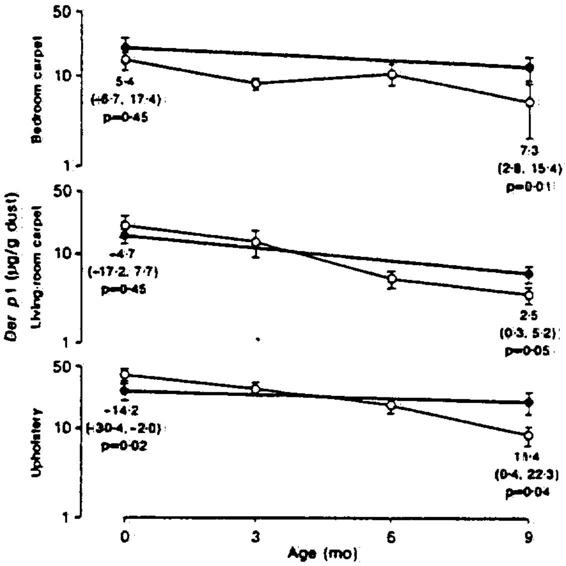
Results

The two groups had similar heredity characteristics, cord-blood IgE distribution, and home environments (table I). Rates of breastfeeding, formula feeding, and introduction of solid foods were similar in the two groups (table II). All infants gained weight satisfactorily; for example, at 3 months the mean (SD) weight was 5·62 (0·84) kg in the prophylactic group compared with 5·73 (0·84) kg in the control group, and at 12 months the groups' respective mean weights were 9·18 (1·15) kg and 9·56 (1·34) kg. The growth pattern of infants fed Aptamil HA from birth was similar to that of the rest of the group (data not shown).

The measures to reduce concentrations of *Der p* I in the homes of the prophylactic group were successful in that the concentrations were significantly lower than those of the control group at 9 months (see figure). In the prophylactic group, the mean *Der p* I concentration for upholstery and living-room and bedroom carpets was 25·9 µg/g dust at birth and 6·0 µg/g dust at 9 months.

By the age of 12 months one or more allergic disorders had developed in 25 (40%) control children and 8 (14%) prophylactic-group children. Although the doctor who made follow-up assessments at 3 and 6 months was aware of group allocation, the pattern was similar (3 months control 18% *vs* prophylactic 5%; 6 months 32% *vs* 12%). Signs of asthma were present at 12 months in 12 (19%) infants in the control group and 4 (7%) of the prophylactic group. The corresponding numbers for eczema were also 12 (19%) and 4 (7%). 7 (11%) control-group infants were classified as having food intolerance, in most to cows' milk or egg, at 12 months. Only 2 (3%) infants in the prophylactic group had food intolerance: in 1 a rash developed when egg was introduced at the age of 7 months; and the other infant had asthma and wheezed after drinking cows' milk when Aptamil HA was stopped at 9 months. 6 (10%) infants in the control group had positive skinprick tests to a range of allergens including housedust mite, cows' milk, egg, wheat, cat, and grass pollen. 2 (3%) infants in the prophylactic group showed positive skinprick tests—1 to egg and 1 to cat dander.

To control for possible effects, despite randomisation, of genetic and environmental factors and to assess the influence



Mean (SEM) *Der p* I concentrations in prophylactic (○) and control (●) groups.

Boxes show mean and (95% CI) difference between groups.

of other risk factors on the development of allergic disorders, we carried out multivariate logistic regression analysis to obtain the adjusted odds ratios for each factor. Logistic regression was done with the presence of any allergic disorder at 3, 6, or 12 months as the dependent variable and all risk factors of interest as independent variables (table III). The process was repeated with individual allergic disorders (at 12 months) as the dependent variables (table IV). After adjustment for other confounding variables, the control group was at significantly greater risk than the prophylactic group for all allergy at each follow-up examination and for asthma and eczema at 12 months. Parental smoking was the other important risk factor irrespective of whether only one or both parents smoked in the house. Maternal smoking was not used as a separate variable, since only 5 mothers smoked and had partners who did not. As expected, maternal allergy, sibling allergy, and male sex were other significant risk factors for total allergy. The prevalence of all allergy at

TABLE III—EFFECT OF RISK FACTORS ON PREVALENCE OF TOTAL ALLERGY

Risk factor	Reference group	Odds ratio (95% CI) 3 mo	6 mo	12 mo
Control group	Prophylactic group	5·64 (1·3–24·2)*	3·98 (1·4–11·5)†	6·34 (2·0–20·1)‡
Parental smoking				
Either	Neither	1·25 (0·2–6·4)	3·36 (1·1–10·7)*	3·97 (1·2–13·6)*
Both	Neither	5·12 (1·2–22·5)*	1·81 (0·5–6·9)	4·72 (1·2–18·2)*
Allergy in				
Mother	No such allergy	2·38 (0·5–11·8)	3·18 (0·9–11·9)	5·92 (1·5–23·0)†
Sibling	No such allergy	1·69 (0·4–6·9)	1·36 (0·5–4·0)	4·59 (1·3–15·8)*
Male	Female	4·17 (1·0–18·3)*	1·93 (0·7–5·5)	1·44 (0·5–4·2)
Low socio-economic group	High socio-economic group	1·43 (0·4–5·4)	1·41 (0·5–4·0)	3·30 (1·1–10·2)*

*p < 0·05, †p < 0·01, ‡p < 0·005, for comparison with reference group.

TABLE IV—EFFECT OF RISK FACTORS ON PREVALENCE OF CERTAIN ALLERGIC DISORDERS AT 12 MO

Risk factor	Reference group	Odds ratio (95% CI)		
		Asthma	Eczema	Food intolerance
Control group	Prophylactic group	4·13 (1·1–15·5)*	3·59 (1·0–12·5)*	3·29 (0·6–17·3)
Parental smoking				
Either	Neither	3·33 (0·8–14·6)	2·35 (0·7–7·9)	1·46 (0·2–9·7)
Both	Neither	11·0† (2·5–48·2)†	0·88 (0·2–5·6)	5·72 (1·1–29·5)*
Sibling allergy	No such allergy	5·71 (1·3–24·5)*	1·39 (0·4–4·5)	0·74 (0·2–3·7)

*p<0·05. †p<0·005.

12 months was higher in infants from the lower than the higher socioeconomic group. Factors tested but found not to be significant, or to change odds ratios for other variables were paternal allergy and the presence of pets (for total allergy), and male sex, maternal or paternal allergy, socioeconomic group, and presence of pets for individual allergic disorders.

Discussion

Since seasonal factors can affect the development of allergic disorders[4,5] we received mothers and their infants for a whole year. A study of the effect of treatment should ideally be double blind, but the nature of the intervention in our study made this ideal impossible. The final assessment by the paediatric allergy specialist was done "blind"; all mothers were briefed before they entered the consulting room not to disclose their group allocation.

At present, allergen avoidance is recommended for treatment but not for prophylaxis of allergic disorders. Because prophylactic measures take much time and effort, only infants at high risk of atopy are suitable for this kind of intervention. Exposure to highly allergenic food and inhalant antigenic protein could prime the immune systems of genetically predisposed infants. Transplacental sensitisation is rare; specific IgE is rarely found in cord blood.[18,19] Two studies[15,20] showed no benefit from food avoidance during the third trimester of pregnancy. Moreover, such avoidance adversely affected weight gain during third trimester and resulted in a slightly lower than expected birthweight for the term infants.

Previous studies[15-17] have shown lower rates of eczema and food reactions when mothers of at-risk infants restrict their diets during lactation. In our study, exposure to allergenic foods, either directly or through mothers' milk, was avoided up to 12 months of age. It is possible that a shorter duration of exclusion is sufficient. Exclusion of the 11 infants whose diets were violated from the analysis did not affect the outcome. In the nursery, cows' milk formula was given inadvertently to a few infants in the prophylactic group. Mistakes were generally avoided by close cooperation with midwives, warning stickers on infants' cots and mothers' beds, and education of mothers to be very vigilant. During the study 16 mothers reported occasional mistakes, such as drinking a cup of tea with milk or giving the infant a manufactured food containing soya or casein. Overall, compliance was very good for such a difficult diet. For mothers who did not wish to breastfeed or who wanted to supplement breastmilk, Aptamil HA was a useful alternative. It is made from soya and collagen and is extensively hydrolysed. The molecular weight of 99% of the molecules is less than 10^4 Da. Similar hydrolysed milk is used for the treatment of cows' milk allergy and can reduce the incidence of eczema and food reactions.[15,17]

Previous studies[15-17] have concentrated on food-allergen avoidance and have reported reductions in eczema and food reactions but not in respiratory symptoms. Inhalant allergens and adjuvants are equally important,[2-4] although more difficult to control. In the UK, housedust mite is the most common allergen in patients with extrinsic asthma and atopic eczema. Chemicals are now available that not only kill the mites but also help to reduce the level of antigen already present in the carpet.[21] Repeated use of one such acaricide in this study gradually reduced antigen concentrations. For prophylaxis, acaricide applications should perhaps be started a few months before the infant is born. The design of our study means that the effect of food and housedust-mite avoidance cannot be separated. Ideally, we should have asked parents in the prophylactic group to give up smoking and to remove furry pets from the house. We did not attempt these interventions for fear of non-compliance, and no advice was offered to either group on pets and smoking in the house.

In infancy, bronchial hyperreactivity manifests as recurrent cough and wheeze, usually after viral respiratory-tract infections. It has been termed recurrent wheezing, wheezy bronchitis, infantile wheezing, and asthma. We prefer to use the term asthma, since many affected infants are later found to be atopic/asthmatic,[22] especially those with genetic predisposition;[23] others, however, disagree with this classification.[24] Sporik and colleagues[6] found that onset of wheezing was earlier in atopic children exposed to high levels of dust-mite antigen in infancy than in those not so exposed. Perhaps in genetically predisposed infants with high allergen exposure, viral respiratory infections and smoking act as adjuvants and lead to persistent bronchial hyperreactivity and asthma.

For practical reasons, open challenge was used for the diagnosis of food intolerance. A double-blind challenge would have been more reliable but management of any adverse food reactions reported by the mother was the same in both groups and blind assessment should have reduced any possible bias. We avoided the term food allergy, since evidence for IgE-mediated food allergy (positive skinprick test to the relevant food antigen) was available in only 30% of cases. A positive skinprick test without signs of allergy (in 1 infant in the prophylactic group, to egg) was not regarded as an allergic manifestation. Chronic "cold" and runny nose were reported in 17 infants (7 prophylactic, 10 control) at 12 months' follow-up. We did not include these signs in the analysis since their aetiology and clinical significance are difficult to establish. No infant with these signs had a positive skinprick test to inhalant allergens.

Individual disorders were two to three times more common in the control than in the prophylactic group and the prevalences of asthma and eczema were higher at 12 months. Parental smoking had a profound effect on the prevalence of asthma and total allergy. In some of the infants asthma may represent transient bronchial hyperreactivity, but we cannot exclude the possibility of continued wheezing in a substantial proportion of these genetically predisposed infants. Advice on parental smoking should be included in any prophylactic regimen against allergic disorders.

We conclude that reduction in exposure of high-risk infants to food and housedust-mite allergens substantially lowers the frequency of allergic manifestations in infancy. Parental smoking contributes greatly to the development of

allergic disorders during infancy, and should be avoided, especially in genetically predisposed families. It is possible that allergen avoidance merely delays rather than prevents the development of allergic disorders.[25] In our study foods were introduced at age 9–12 months in the prophylactic group and only 1 infant reacted to cows' milk. Longer follow-up is required, at least into later childhood, to find out whether the reduction in allergic manifestations will be maintained. Because of their high prevalence, allergic disorders are a huge burden to personal and family life and a substantial health-care cost. If the benefit shown in this study is maintained, it is likely to outweigh the costs of dietary supervision, hypoallergenic formulae, and antidust-mite measures.

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Effects of topical nasal anaesthesia on shift of breathing route in adults

TAKASHI NISHINO AYAKO SUGIYAMA ATSUKO TANAKA
TERUHIKO ISHIKAWA

The position of the soft palate is known to determine the breathing route, but the physiological mechanisms that bring about a shift from nasal to oral breathing are unclear. To test the hypothesis that activation of receptors in the nasal passage may be involved in reflex initiation of oral breathing after nasal obstruction, we investigated respiratory responses to nasal occlusion before and after topical lignocaine anaesthesia of the nasal passages.

Eleven volunteers were fitted with custom-made partitioned face masks, which separated nasal and oral passages. Air flow through each passage was detected by changes in airway pressure and carbon dioxide concentration. Nine subjects were habitual nasal breathers both before and after topical anaesthesia with 4% lignocaine. Among these subjects, the time to initiate oral breathing in response to nasal occlusion was significantly shorter before anaesthesia than afterwards (mean 4·4 [SD 2·5] *vs* 10·8 [7·4] s, $p<0·01$). Similarly, the time to resume nasal breathing after release of nasal occlusion was significantly shorter before topical anaesthesia than afterwards (6·9 [4·9] *vs* 12·1 [7·8] s, $p<0·01$). Topical anaesthesia did not affect respiration rate, end-tidal carbon dioxide concentration, or arterial oxygen saturation.

These findings suggest that in human beings sensory information from receptors in the nasal passage has an important role in controlling the shift of breathing route.

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ADDRESS: Department of Anesthesiology, National Cancer Center Hospital, Tsukiji 5-1-1, Chuo-ku, Tokyo 104, Japan (T. Nishino, MD, A. Sugiyama, DDS, A. Tanaka, MD, T. Ishikawa, MD). Correspondence to Dr Takashi Nishino.

Butz, A.M., and Rosenstein, B.J., "Passive Smoking Among Children with Chronic Respiratory Disease," Journal of Asthma 29(4): 265-272, 1992.

The authors of this study sought to determine the prevalence and source of passive smoke exposure among children with chronic respiratory diseases and to compare these children to both a well-child and nonrespiratory chronic illness child population. Children with asthma, cystic fibrosis, and rheumatoid arthritis were all compared with well children. The authors reported that a third of all children surveyed (chronically ill and well) were exposed to passive smoke on a daily basis.

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Passive Smoking Among Children with Chronic Respiratory Disease

Arlene M. Butz, R.N., Sc.D.* and Beryl J. Rosenstein, M.D.†

*The Johns Hopkins University Schools of *Nursing and †Medicine*
Department of Pediatrics
Baltimore, Maryland

ABSTRACT

· The purpose of this study was to determine the prevalence and source of passive smoke exposure among children with chronic respiratory diseases and compare these to both a well child and nonrespiratory chronic illness child population. Rates and source of passive smoke exposure were compared among four child groups: asthma, cystic fibrosis, rheumatoid arthritis, and well children using a questionnaire mailed to the parents of the selected children. Twenty percent of respondents reported current smoking with a significantly higher rate among the cystic fibrosis and rheumatoid arthritis groups. One-third of all children surveyed were exposed to passive smoke at home and/or day care on a daily basis. Over 80% of the asthma and cystic fibrosis respondents reported a change in smoking behavior (i.e., smoking outside the home or smoking fewer cigarettes) after the diagnosis of their child's illness as compared with only 40% of the nonrespiratory groups. Health care providers need to inquire about potential sources of passive smoke exposure in their patients, particularly children with chronic respiratory disease.

Address for reprints: Arlene M. Butz, R.N., Sc.D., Assistant Professor, The Johns Hopkins University, School of Nursing, 600 N. Wolfe Street, Baltimore, MD 21205.

INTRODUCTION

In 1986 the Surgeon General and the National Academy of Sciences reported that passive smoking by nonsmokers, including children, can cause significant morbidity (1,2). Numerous studies have documented the adverse effects of parental cigarette smoking on children including; increased occurrence of respiratory illness (3–8), decreased pulmonary function (9), and increased physician visits (10), hospitalization rates (11,12), and emergency room (ER) visits (13). A dose-dependent relationship between the estimate of passive smoke exposure and overall severity of disease based on hospital admissions, growth, nutrition, and peak expiratory flow rates, has been demonstrated in children with cystic fibrosis (14).

Approximately 29% of adults in the United States currently smoke cigarettes (15) and 70% of children live in homes where there is at least one adult smoker (16). Tobacco smoke is ubiquitous in public areas and exposure to environmental tobacco smoke is unavoidable in these settings. However, there are no studies which quantitate the daily exposure to passive smoke among children with chronic respiratory illnesses, including asthma (AS) and cystic fibrosis (CF).

The primary objective of the present study was to determine the prevalence and source of passive smoke exposure among children with chronic respiratory diseases including AS and CF and to compare these to both a well child and nonrespiratory chronic illness child population. Passive smoke exposure was defined as daily involuntary inhalation of cigarette smoke by a child either in their home or in a day care/child care setting. We hypothesized that children with chronic respiratory diseases would be less exposed to passive smoke than the well child and nonrespiratory illness groups due to parental awareness of the adverse respiratory effects of passive smoke exposure.

METHODS

Study Population and Procedures

The study was cross-sectional in design and was conducted by a mailed parent questionnaire (available upon request) to four groups: asthma (AS), cystic fibrosis (CF), rheumatoid arthritis (RA), and well children (WELL). The CF and RA patients, primarily caucasian and with private health insurance, were recruited from hospital-based outpatient specialty clinics in order to obtain an adequate sample size. Most AS and WELL patients attending hospital-based clinics were from families of low socioeconomic status (SES). Therefore, in order to select a group of patients of comparable SES, the AS and WELL groups were recruited from private pediatric practices in the same metropolitan area. Questionnaires were mailed to each group with the following distribution: AS 175, CF 154, RA 134, and WELL 171 for a total mailing of 634 questionnaires. Approval for the study was obtained from the Joint Committee on Clinical Investigation of the Johns Hopkins Medical Institutions.

Parent questionnaires were mailed between June and October 1989. Information was obtained on sociodemographic characteristics, household members' smoking habits, childrens' passive smoke exposure at day care and afterschool programs, and change in smoking behavior or smoking cessation attempts of respondent (RES) smokers.

A SES rating was assigned to each family based on the respondent's or head of household's income, educational level, and occupation. Two levels of SES were defined. Low SES was defined as (a) gross income less than $30,000, (b) less than high school education, or (c) semiskilled or unskilled labor occupation or receipt of public assistance. High SES included all other respondents. The income level criterion of $30,000 was selected based on the income distribution of the

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sample. Seventy-three percent of RES reported an income greater than $30,000 which was the upper level used on the questionnaire. Because of the skewed distribution of income level, the classification of low SES is relative to other subjects in this sample.

All RES were asked "Have you every smoked?" as well as ascertainment of smoking habits of other family members, relatives, and visitors, including number cigarettes smoked and smoking location in household. Respondents who reported current smoking were asked "Have you changed your smoking habits since your child was diagnosed with his/her disease or since having children?," and "Have you ever tried to stop smoking?"

To increase the response rate, a fast food coupon was enclosed with each survey and a second mailing was conducted within two months of the initial mailing. Telephone follow-up of nonrespondent CF families was conducted at the end of three months to compare smoking prevalence of nonrespondents and RES. Only the CF group was selected for follow up due to resource constraints.

Statistical Analyses

Mean baseline RES characteristics, parental smoking habits and passive smoke exposure among child groups were compared using Chi-square analysis, Student's t-test, and analysis of variance (ANOVA). Chi-square analysis was used to compare SES levels among the groups. Multivariate logit (logarithm of the odds) analyses were performed to estimate the likelihood of passive smoke exposure among the four groups. Using the multivariate logistic regression technique, the combined effects of age, gender, SES, and child group can be examined simultaneously for their association with passive smoke exposure in the child. After several logistic models were tested, a final set of parameters was selected based on significant bivariate association with passive smoke exposure and clinical significance. The final model tested to predict passive smoke exposure included the independent variables: RES gender, education, income and child group and age. All analyses were carried out using the SAS computer package (17).

RESULTS

Population Characteristics

The response rate varied by child group; AS 102/175 (58%), CF 103/154 (66.9%), RA 50/134 (37.3%), and WELL 105/171 (61%). The overall response rate was 360/634 (56.8%). Respondents tended to be white (94.3%), female (63.7%), and married (86.9%) with a mean age of 38.4 years (Table 1). The mean age of the index child was 9.3 years. Over three-quarters of RES (78.9%) reported a high school education and 51.6% reported a college education. Median household income was over $30,000. Respondent age, gender, education level, marital status, income, and occupation differed significantly by child group (Table 1). The CF and RA groups had significantly more low SES families as compared to the AS and WELL groups (CF 48.4%, RA 48%, AS 33.3%, WELL 24.8%, X^2 = 15.77, p = .001) (Table 1).

Smoking Characteristics

Current smoking (within the last month) was reported by 20.3% (73/360) of RES (Table 2) with a significant difference among the groups (p = .008). Among all RES, there was no difference in smoking frequency by gender (χ^2 = 5.33, p = .149). The CF and RA groups reported the highest current smoking rates (29.1% and 28%, respectively). Current smokers reported smoking a mean of 16.7 cigarettes per day and smoking for a mean of 16.6 years (Table 3). There were no significant differences among the groups for these parameters. The percentage of nonsmokers (never smoked) (44.4%) and ex-smokers (35.3%) did not differ significantly by group (nonsmokers, χ^2 = 5.2, p = .157; ex-smokers χ^2 = 1.9, p = .603) (Table 2). Previous attempts to stop smoking were reported by 79.5% (58/73) of the current smokers (Table 3) and did not differ significantly among the groups (χ^2 = 5.1, p = .167). Most quitters

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Table 1. Baseline Variables for Total Respondent Sample and for Each Child Group

	AS	CF	RA	WELL	TOTAL	p VALUE
Sample size	102	103	50	105	360	
Age (years)	39.7	37.9	41.5	36.1	38.4	$F = 3.36$
Mean ± SD	(±12.3)	(±11.6)	(±14.4)	(±6.2)	(±11.1)	$p = .019$
Females (%)	72.6	65.1	76.0	47.6	63.7	$X^2 = 18.4$ $p < .001$
White (%)	93.9	96.0	89.8	95.2	94.3	$X^2 = 5.7$ $p = .463$
Married (%)	92.2	75.7	86.0	93.3	86.9	$X^2 = 16.1$ $p = .001$
High school education (%)	89.2	67.9	60.0	88.6	78.9	$X^2 = 52.9$ $p < .001$
Income > $30,000 (%)	77.5	63.1	66.0	80.9	72.8	$X^2 = 13.9$ $p = .03$
Professional occupation (%)	48.5	44.6	22.6	59.8	48.4	$X^2 = 18.6$ $p = .03$
SES (low) (%)	33.3	48.5	48.0	24.8	37.2	$X^2 = 15.8$
(high) (%)	66.7	51.5	52.0	75.2	62.8	$p = .001$

Table 2. Smoking Variables for Total Respondent Sample and for Each Child Group

	AS	CF	RA	WELL	TOTAL	p VALUE
Sample size	102	103	50	105	360	
Nonsmokers	47	37	22	54	160	$X^2 = 5.2$
(Never smoked)	(46.1%)	(35.9%)	(44.0%)	(51.4%)	(44.4%)	$p = .157$
Ex-smokers	40	36	14	37	127	$X^2 = 1.9$
	(39.2%)	(34.9%)	(28.0%)	(35.2%)	(35.3%)	$p + .603$
Current	15	30	14	14	73	$X^2 = 11.9$
smokers	(14.7%)	(29.1%)	(28%)	(13.3%)	(20.3%)	$p = .008$

Table 3. Current Smokers: Smoking Variables and Quit Attempts by Child Group

	AS	CF	RA	WELL	TOTAL	p VALUE
Proportion of current smokers	15/102	30/103	14/50	14/105	73/360	$X^2 = 11.9$ $p = .007$
Number of cigarettes/day[a]	17.5 ± 10.8	14.6 ± 9.5	18.3 ± 9.1	18.9 ± 17.4	16.7 ± 11.5	$F = .59$ $p = .63$
Number of years smoked[a]	16.3 ± 6.6	16.1 ± 7.5	17.1 ± 9.9	17.0 ± 4.2	16.6 ± 7.2	$F = .20$ $P = .89$
Number of respondents who changed[b] smoking behavior after diagnosis or after child born (excluding quit attempts)	12/15 (80%)	25/30 (83.3%)	4/14 (28.6%)	7/14 (50%)	48/73 (66%)	$X^2 = 12.4$ $p = .006$
Quit attempts	11/15 (73%)	21/30 (70%)	13/14 (92.9%)	13/14 (92.9%)	58/73 79.5%)	$X^2 = 5.1$ $p = .167$

[a]Mean ± SD.
[b]Changes included: smoke outside household, decrease number of cigarettes, smoke only at work, or smoke only at night.

(76%) reported using no structured smoking cessation program, but rather stopped "cold turkey" on their own. Furthermore, only a third (34%) of quitters reported stopping for longer than one year.

Prevalence of Passive Smoke Exposure by Study Group

Thirty percent of all RES reported one or more smokers in the household on a regular basis (Table 4); 12% of RES had two or more smokers per household. Households with one or more smokers were reported significantly more often by the CF and RA respondents ($\chi^2 = 9.24$, $p = .03$) (Table 4). Exposure to smoke in a day care setting was reported by 18.4% of all families; there was no significant difference by group. Daily passive smoke exposure, either in the household or day care/after care, was reported by a third of all RES (Table 4) and differed significantly by child group ($\chi^2 = 12.02$, $p = .007$). Both the CF and RA groups reported higher daily passive smoke exposure rates as compared with the AS and WELL groups. Passive smoke exposure also differed by SES group. Among the high SES respondents, there were no significant differences by group between the daily passive exposure rates ($\chi^2 = 4.43$, $p = .22$). However, among the low SES respondents, the CF and RA groups reported significantly higher rates of daily passive smoke exposure as compared with the AS and WELL groups ($\chi^2 = 9.68$, $p = .02$).

Factors associated with passive smoke exposure examined by logistic regression are shown in Table 5. In the CF and RA groups, less education independently predicted passive smoke exposure. Child's age was also associated with passive smoke exposure, i.e., younger age was associated with more passive smoke exposure. Respondent's gender and income did not predict passive smoke exposure. There were no significant correlations ($r < .32$) between any of the selected variables in the final logistic model. All interaction terms were statistically nonsignificant in the tested logistic models.

Change in Smoking Behavior

Sixty-six percent (48/73) of current smokers reported a change in smoking behavior following a diagnosis of their child's disease or the birth of their index child (Table 3). Thirty percent (22/73) of current smokers reported no change in smoking behavior following the diagnosis of their child's disease. Smoking behavior information was not available for three smokers. Parents of children with AS and CF reported a significantly higher rate of

Table 4. Passive Smoke Exposure: Number and Type of Exposures by Child Group

	AS	CF	RA	WELL	TOTAL	p VALUE
Sample size	102	103	50	105	360	
Type of exposure						
1 or more current household smokers	28/102 (27.5%)	40/101 (39.6%)	17/50 (34%)	22/105 (20.9%)	107/358 (29.9%)	$X^2 = 9.24$ $p = .03$
Exposed to smoker in daycare	3/21 (14.3%)	7/23 (30.4%)	1/9 (11.1%)	5/34 (14.7%)	16/87 (18.4%)	$X^2 = 10.08$ $p = .34$
Daily passive[a] exposure (All SES groups)	28/102 (27.5%)	46/103 (44.7%)	18/50 (36%)	25/105 (23.8%)	117/360 (32.5%)	$X^2 = 12.02$ $p = .007$
Daily passive[a] exposure (High SES groups)	16/68 (23.5%)	20/53 (37.7%)	5/26 (19.2%)	20/79 (25.3%)	61/226 (26.9%)	$X^2 = 4.43$ $p = .22$
Daily passive[a] exposure (Low SES groups)	12/34 (35.3%)	26/50 (52%)	13/24 (54.2%)	5/26 (19.2%)	56/134 (41.8%)	$X^2 = 9.68$ $p = .02$

[a]Household and/or day care smoke exposure.

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Table 5. Logistic Regression Results of Sociodemographic Characteristics and Child Group on Passive Smoke Exposure

	ESTIMATE BETA	STANDARD ERROR OF BETA	ODDS RATIO	95% CI
Intercept	4.355	1.14	–	–
Gender (RES)	–.250	.265	.78	.46, 1.31
Education (RES)	–.585	.154	.56	.41, .75[b]
Income (RES)	–.278	.179	.76	.53, 1.07
Child's age	–.051	.025	.95	.90, .99[a]
Child group	–.246	.120	.78	.62, .99[a]

Model X^2 = 34.45 with 5 df, $p < .0001$
[a]$p < .05$.
[b]$p < .001$.

change in their smoking habits (i.e., smoke outside the household or smoking fewer cigarettes) as compared with the RA and WELL groups ($\chi^2 = 12.4$, $p = .006$) (Table 3).

The most frequently reported modifications in smoking behavior were a combination of smoking in another room or outside the home away from the child and smoking fewer cigarettes (41.3%), smoking outside the household only (28.3%) and smoking fewer cigarettes only (13%). Other changes such as smoking only at night, smoking only at work, smoking in another room away from the child, or using an air purifier in the home were reported by 17.4% of smokers who changed behavior.

Table 6. Type of Change in Smoking Behavior Reported by Current Smokers (n = 46)

TYPE OF CHANGE	NUMBER	PERCENT
Smoke outside of household	13	28.3
Decrease the number of cigarettes smoked	6	13.0
Smoke in another room away from child	5	10.9
Smoke only at work	1	2.2
Smoke only at night after children in bed	1	2.2
Smoke in house, but use air purifier	1	2.2
Combination of smoking in another room or outside the home and decreasing number of cigarettes	19	41.2
	46	100%

Smoking Patterns of Nonresponders

Of the 51 CF nonrespondents, 39 (76.5%) were contacted by telephone and responded to a brief smoking survey ascertaining only parental and household smoking proportions. Parental smoking was reported by 39.2% of the nonrespondents compared to 29% of the CF respondents. Household smoking was reported by 63% of CF nonrespondents as compared with 40% of the CF respondents ($\chi^2 = 6.38$, $p = .01$).

DISCUSSION

The proportion of RES in the study who reported current smoking (20.3%) is lower than both the national (29%) and Maryland (23.9%) rates of current smokers (18). This lower rate may reflect reluctance by parents of children with a chronic disease to disclose smoking behavior. The prevalence of smoking in CF nonrespondents (39.2%) was higher than in RES (29.1%) which would increase the actual rate of passive smoke exposure in the CF and perhaps the AS groups. The higher rate of smoking in the CF nonrespondents may reflect self-selection bias. However, the household smoking rate of 45.7% (65/142) among combined CF respondents and nonrespondents is comparable to the 56% household smoker rate previously reported in CF families (14). In our CF sample, smokers were less likely to respond to the questionnaire. However, during a telephone interview

they did reveal their smoking behavior yielding a higher rate of current smokers. This suggests that underreporting of smoking is likely the case in our data, tending to underestimate the true risk of passive smoke exposure in patients with a chronic respiratory illness. One limitation of our data is lack of follow up of other nonrespondents. This would determine if parents of children with a respiratory disease are less likely to respond to a smoking questionnaire as compared to parents of children diagnosed with a nonrespiratory disease.

Differences in current smoking rates varied among the disease groups with the CF and RA groups reporting a significantly higher frequency of passive smoke exposure in their homes. Smoking characteristics, including number of cigarettes smoked per day and number of years smoked as reported by current smokers, did not differ by disease group.

Socioeconomic differences most likely explain the higher rates of smoke exposure among the patients in the CF and RA groups. There were significantly higher numbers of RES in the CF and RA groups who had low SES (Table 1). When the SES levels were combined, daily passive smoke exposure was significantly higher in the CF and RA groups (Table 4). However, these differences disappeared when the high SES respondents were examined separately. Among low SES respondents, daily passive smoke exposure remained higher in the CF and RA groups. Lower education was the only SES factor which independently predicted passive smoke exposure in the sample controlling for RES age, gender, occupation, income, and child's age (odds ratio, .55; 95% CI, .41, .75) (Table 5). This is consistent with National Health Interview survey data in which the prevalence of smoking was higher among lower SES persons, and smoking prevalence decreased with increased years of education and household income (15). Even after controlling for the unequal distribution of income in the four groups, lower education was the strongest predictor of parental smoking. Racial differences in smoking patterns were not apparent due to the homogeneity of our sample.

Self-reported cigarette consumption is generally reliable (19). Previous reports of a strong dose-dependent relation between self-reported tobacco smoke exposure and salivary and urinary continine levels support the reliability of self-reported cigarette consumption (20). A comparison of adjusted consumption data from cigarette excise taxes (U.S. Department of Agriculture) and self-reported cigarette consumption as reported from National Health Interview Surveys (NHIS) was consistent, supporting the reliability of self-reported smoking data (19). Expected bias in our data would be the underrepresentation of smokers, thereby reducing the true proportion of smokers in each group. Therefore, our data probably reflect the minimal level of smoking in this population.

Other sources of passive smoke exposure including day care and after school care are consistent with recent reports of passive smoke exposure in neonates attending day care (21). The finding that 18.4% of all children and 30.4% of CF patients in our sample attended a day care facility in which they were exposed to a smoker warrants increased public awareness and action. Regulation of worksite smoking policies should include day care and after school personnel in order to reduce a significant source of passive smoke exposure in children. At a minimum, parents must request that a no smoking policy be implemented in day care settings.

It is encouraging that more than 80% (37/45) of the AS and CF respondents reported a change in their smoking behavior after the diagnosis of their child's illness as compared with only 39.3% (11/28) of the combined RA and WELL respondents (Table 3). Eighty percent of all current smokers reported at least one unsuccessful attempt to quit (Table 3).

Based on the evidence that passive smoke exposure causes increased morbidity and decreased pulmonary function in patients with AS (22-24) and CF (14), it is disturbing that 44.7% of CF patients and 27.5% of AS patients in our sample reported daily passive smoke exposure and that 30.1% (22/73) of the children in our sample reside in a household with parents who smoke and report no change in their smoking behavior. Health care providers need to stress the importance of ascertaining the smoking status of day care personnel as well as other household contacts and

to encourage attempts to quit by household members who smoke (25).

SUMMARY AND CONCLUSIONS

In conclusion, our data indicate that a third of all children surveyed (chronically ill and well) are exposed to passive smoke on a daily basis including home and day care settings. Health care providers should inquire about potential sources of passive smoke exposure in their patients, particularly children with chronic respiratory disease, and counsel them accordingly.

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The authors of this study examined the possible relationship between parental smoking and both subsequent development of asthma and subsequent lung function (before age 12) in approximately 700 children enrolled before age five. The authors report that children of smoking mothers with 12 or fewer years of education and who smoked 10 or more cigarettes per day were 2 1/2 times as likely (95% CI: 1.42 to 4.59) to develop asthma than children of mothers with the same level of education who did not smoke or who smoked fewer than 10 cigarettes a day. The children also reportedly had 15.7% lower maximal midexpiratory flow. There was no association between maternal smoking and asthma or lung function in children of mothers with more than 12 years of education.

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Increased Incidence of Asthma in Children of Smoking Mothers

Fernando D. Martinez, MD[*‡]; Martha Cline, MS[*]; and Benjamin Burrows, MD[*§]

ABSTRACT. The relationship between parental smoking and both subsequent development of asthma and subsequent lung function (before age 12) was studied in more than 700 children enrolled before age 5. Children of mothers with 12 or fewer years of education and who smoked 10 or more cigarettes per day were 2.5 times more likely (95% confidence interval 1.42 to 4.59; $P = .0018$) to develop asthma and had 15.7% lower maximal midexpiratory flow ($P < .001$) than children of mothers with the same education level who did not smoke or smoked fewer than 10 cigarettes per day. These relationships were independent of self-reported respiratory symptoms in parents. There was no association between maternal smoking and subsequent incidence of asthma or maximal midexpiratory flow among children of mothers with more than 12 years of education. It is concluded that children of lower socioeconomic status may be at considerable risk of developing asthma if their mothers smoke 10 or more cigarettes per day. It is speculated that recently reported increases in prevalence of childhood asthma may be in part related to the increased prevalence of smoking among less educated women. *Pediatrics* 1992;89:21-26; *asthma, tobacco smoke pollution, maternal education, childhood.*

ABBREVIATIONS. FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; $FEF_{25\%-75\%}$, maximal midexpiratory flow.

There is increasing evidence suggesting that parental smoking (especially maternal) may be associated with an increased prevalence of respiratory symptoms in infants and toddlers.[1] In older children of smoking parents, reduced levels of lung function[2] and an increased prevalence of airway hyperresponsiveness[3] and skin test reactivity to aeroallergens[3] have also been reported. However, the possible role of maternal smoking in inducing childhood asthma is controversial and not all studies have observed significant effects (reviewed in Ref. 4). This has been attributed to the small size of the observed effects; reductions in spirometric parameters, for example, are on the order of 1% to 5%, values that have been considered unlikely to lead to clinically serious compromise in lung function.[4] Also, most reports dealing with this issue are from cross-sectional surveys[5] and it has been shown[6] that results of this type of study may be confounded by the concurrent relationships of symptoms in children to other familial factors, particularly a relation of reported children's symptoms to parents' symptoms.

It has been recently observed that prevalence and changes in prevalence of smoking in women are highly dependent on level of education.[7] Differences in smoking habits of subjects with less education vs those with more education may influence the effects of maternal smoking on their children's health. However, socioeconomic level is seldom considered as an effect modifier in studies of parental smoking and respiratory status in children. Authors often report results of multivariable analyses after adjusting for maternal education, paternal occupation, or other indices of socioeconomic level. These procedures are efficient in controlling for confounding but they may also conceal important differences in effect between strata. It is reasonable to assume that the degree of exposure to environmental cigarette smoke may be different for children whose parents have different educational backgrounds.[8] If these differences could be demonstrated, they may at least partially explain the different results obtained in studies of the effects of parental smoking on the respiratory health of their children.

It is also important to consider the fact that most available studies rely either only on parental reports and physicians' diagnoses or only on physiologic measures as outcomes. For the former, interpretation of results may be influenced by the reliability and degree of standardization of the questionnaires used,[5] while for the latter, the clinical significance of small changes in physiologic parameters remains unknown.

The aim of this longitudinal study was to determine the relationship of parental smoking at enrollment (before age 5) to both subsequent incidence of asthma and subsequent lung function in a random sample of children.

SUBJECTS AND METHODS

The subjects of this study are enrollees of the Tucson study of chronic obstructive lung disease.[9] Details of enrollment procedure have been given elsewhere.[9] A random, stratified, cluster sample of white, non-Mexican-American households in Tucson, Arizona, was first studied in 1972 to 1973. During subsequent follow-up surveys (nine had been completed by April 1988), all new members of each selected household were automatically enrolled into the study. The subjects of this study are the 786 subjects who were younger than 5 years of age on enrollment into the study at its inception (survey 1, starting in February 1972) or at any subsequent survey and who had at least one follow-up questionnaire available before age 12. Seventy-five percent of these children were enrolled before age 2. Mean age at the last questionnaire available was 7.4 years for those enrolled before 12 months, 7.7 years for those

From the * Respiratory Sciences Center and the Departments of ‡ Pediatrics and § Internal Medicine, University of Arizona College of Medicine, Tucson.
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Reprint requests to (F.D.M.) Division of Respiratory Sciences and Department of Pediatrics, Arizona Health Sciences Center, Tucson, AZ 85724.
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enrolled between the ages of 1 and 3 years, and 8.5 for those enrolled between the ages of 3 and 5 years.

Information about cigarette smoking habits and respiratory symptoms among parents was obtained at the time of enrollment of their children. Questions about smoking focused on each parent separately.

Standardized questionnaires on respiratory symptoms were used to ask parents whether they had recurrent wheeze or chronic cough.[9] Mothers also reported the number of years of formal education, and they were classified in two groups: with (>12 years) or without more than a high school education (≤12 years). We chose this variable as an index of socioeconomic status because previous studies have shown that other more complex indices of socioeconomic level add little to or even obscure the relationships observed between level of education and level of lung function or prevalence of respiratory disease.[10]

The main outcome variable for this study was the development of asthma during follow-up. Children who already had a diagnosis of asthma at enrollment (n = 12) were not included. A question of the general form "Has this child been seen by a doctor for asthma in the past year?" was included in all follow-up surveys. Children were considered to have a new diagnosis of asthma from a certain age (called hereafter "incidence of asthma") if they had not seen a physician for this diagnosis previously and, at that age, they had seen a physician for the disease.

For children aged 6 or older, lung function was measured in all but one survey using standard flow-volume curves.[11] Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and maximal midexpiratory flow ($FEF_{[illegible]}$) were derived from forced expiratory maneuvers as described earlier.[11] For the purpose of this report, the last lung function test available before age 12 for each subject (n = 316) was used.

Relative risks and their confidence intervals and attributable risks were calculated with the techniques described by Rothman.[12] Pooled point estimation of a uniform effect for stratified cumulative incidence data was assessed both by maximum likelihood and by use of an extension of the Mantel-Haenzel estimators.[12] Analysis of variance and standard *t* tests were used when lung function was the outcome variable.

RESULTS

There were 89 new cases of physician-diagnosed asthma among 774 subjects at risk (cumulative incidence of 11.5%). More than two thirds of these subjects were boys (60/89; $P < .01$). Thirty-five subjects had no information about maternal smoking, and no information about paternal smoking was available for 74 subjects. Mothers and fathers were originally classified as current smokers, ex-smokers, and never-smokers. Since there was no significant difference in any outcome variable between ex-smokers and nerver-smokers (data not shown), these two groups were combined. Mothers who said they were current smokers were classified as light (<10 cigarettes per day) or moderate/heavy (≥10 cigarettes per day) smokers. Only 21 (2.7%) mothers were light smokers, whereas 146 (18.6%) mothers smoked 10 or more cigarettes per day. Also, because results (not shown) for children of mothers who were light smokers were very similar to those of never-smokers (n = 441) and ex-smokers (n = 134), these three groups were combined. Table 1 shows the risk of developing asthma during follow-up by maternal and paternal smoking at enrollment. Children of mothers who smoked 10 or more cigarettes per day were almost 70% more likely to have physician-diagnosed asthma than children of mothers who did not smoke or smoked fewer than 10 cigarettes per day ($P = .015$). Conversely, there was no relationship between paternal smoking and subsequent incidence of asthma.

Children of parents who reported having recurrent wheeze or chronic cough at enrollment of their children (n = 405) were almost 3 times more likely than the remainder of the cohort to have physician-diagnosed asthma (gender-adjusted relative risk = 2.94, 95% confidence interval 1.85 to 4.68; $P < .0001$). Table 2 shows the relationship of mothers' smoking habits to incidence of asthma in their children stratified by gender and by parental symptoms. The risk of developing asthma was still almost 60% higher among children of mothers who smoked 10 or more cigarettes per day after adjusting for gender and parental symptoms (relative risk = 1.59, 95% confidence interval 1.03 to 2.44; $P = .036$). The small number of daughters of nonsmoking mothers with symptoms did not allow for a meaningful comparison within this group. There was no significant difference in the effects of maternal smoking on incidence of asthma between the four groups (boys and girls with and without parental respiratory symptoms, respectively) described in Table 2 (χ^2 for heterogeneity = 3.3; $df = 3$; $P = .6$).

Maternal education had no independent effect on cumulative incidence of asthma (unadjusted relative risk of 1.12 and gender-adjusted relative risk of 0.99 when 310 children whose mothers had ≤12 years of formal education were compared with 428 children of mothers with more than high school education; $P = .9$ and 1.0, respectively). However, mothers with 12 or fewer years of formal education were twice as likely to be current smokers than mothers with higher education (27.7% vs 13.3%, $P < .0001$). Within smokers, however, number of cigarettes smoked daily was not significantly higher in less educated mothers than in mothers with more than 12 years of education (20.6 ± 10.9 vs 20.2 ± 8.7; $P = .8$). Table 3 shows the relative risk of physician-diagnosed asthma by maternal smoking at enrollment and by maternal education. Maternal smoking had different effects on cumulative incidence of asthma depending on the level of maternal education. Among children of less educated mothers, the gender-adjusted risk of developing asthma was 2.55 (95% confidence interval 1.42 to 4.59; $P = .0018$) times higher when the mother smoked 10 cigarettes or more than when the mother smoked fewer than 10 cigarettes or did not smoke. The attributable proportion (ie, the proportion of all cases of asthma occurring among children of less educated mothers that is attributable to maternal smoke exposure) was 30.0%. These relationships persisted after stratifying by any parental respiratory symptoms (adjusted relative risk = 2.25, 95% confidence interval = 1.24 to 4.1; $P = .008$). On the contrary, maternal smoking did not significantly increase the risk of developing asthma among children of mothers with more than 12 years of education (gender-adjusted relative risk = 1.03, 95% confidence interval 0.61 to 1.75; $P = .9$). Paternal smoking did not increase the likelihood of developing asthma either in children of less educated or of more educated mothers.

Daughters of smoking mothers had significantly larger FVC values than daughters of nonsmoking mothers (Table 4; $P = .018$). Children of both genders

TABLE 1. Relationship Between Mothers' and Fathers' Smoking at Enrollment and Subsequent Development of Asthma in Their Children*

	Boys			Girls			RR Adjusted for Gender (95% CI)
	n	% With Asthma	RR	n	% With Asthma	RR	
Mother							
Smokes ≥ ½ pack/d	80	21.3	1.63	63	12.7	1.78	1.68† (1.10–2.58)
Nonsmoking or < ½ pack/d	315	13.0		281	7.1		
Father							
Smokes ≥ ½ pack/d	102	13.7	0.95	85	9.4	1.35	1.06 (0.67–1.69)
Nonsmoking or < ½ pack/d	269	14.5		244	7.0		

* Information about maternal smoking was not available for 35 children, and 74 subjects had no data on paternal smoking. RR, relative risk; CI, confidence interval.
† $P = .018$.

TABLE 2. Relationship of Mothers' Smoking Habits to Incidence of Asthma in Their Children by Parental Respiratory Symptoms and by Gender*

Parental Symptoms	Maternal Smoking	Boys			Girls		
		n	% With Asthma	RR	n	% With Asthma	RR
Yes	Nonsmoker or < ½ pack/d	180	17.0	1.47	134	10.4	2.07
Yes	≥ ½ pack/d	54	25.9		37	21.6	
No	Nonsmoker or < ½ pack/d	135	6.7	1.80	146	4.1	†
No	≥ ½ pack/d	25	12.0		25	0.0	

* Information about maternal smoking was not available for 35 children. Three additional subjects had no data on parental respiratory symptoms. RR, relative risk. The relative risk (95% confidence interval) of developing asthma by maternal smoking adjusted for gender and parental symptoms was 1.59 (1.03 to 2.44) ($P = .036$).
† Not calculable

TABLE 3. Relationship of Mothers' Smoking Habits to Incidence of Asthma in Their Children by Maternal Education*

Maternal Education	Maternal Smoking	Boys			Girls			RR Adjusted for Gender (95% CI)
		n	% With Asthma	RR	n	% With Asthma	RR	
> 12 y	Nonsmoker or < ½ pack/d	198	14.1	0.86	173	8.7	1.44	1.03 (0.61–1.75)
> 12 y	≥ ½ pack/d	33	12.1		24	12.5		
≤ 12 y	Nonsmoker or < ½ pack/d	117	11.1	2.50	107	4.7	2.71	2.55† (1.42–4.59)
≤ 12 y	≥ ½ pack/d	47	27.7		39	12.8		

* Information about maternal smoking was not available for 35 children. One additional subject had no quantitative data on maternal smoking. RR, relative risk; CI, confidence interval.
† $P = .0018$.

TABLE 4. Lung Function in Children (as Percent Predicted) by Maternal Smoking at Enrollment by Gender*

Lung Function/Maternal Smoking	Boys		Girls	
	Mean ± SD (n)	P	Mean ± SD (n)	P
FVC				
Nonsmoker or < ½ pack/d	100.7 ± 13.2 (145)	.5	98.1 ± 12.7 (111)	.018
≥ ½ pack/d	101.0 ± 13.1 (38)		105.3 ± 13.2 (22)	
FEV_1				
Nonsmoker or < ½ pack/d	100.1 ± 12.8 (145)	.2	98.4 ± 12.7 (111)	4
≥ ½ pack/d	97.7 ± 11.8 (38)		100.9 ± 13.4 (22)	
$FEF_{25-75\%}$				
Nonsmoker or < ½ pack/d	98.6 ± 23.3 (145)	.007	99.1 ± 23.3 (111)	11
≥ ½ pack/d	88.5 ± 20.0 (38)		90.3 ± 24.4 (22)	

* FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; $FEF_{25-75\%}$, maximal midexpiratory flow.

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whose mothers smoked 10 or more cigarettes per day had lower values for percent predicted $FEF_{25\%-75\%}$ compared with children of mothers who were nonsmokers or smoked fewer than 10 cigarettes per day, although differences reached statistical significance only for boys. Introduction of any parental respiratory symptoms as a covariate did not affect the relationship between maternal smoking and the lung function parameters described above.

We also studied the relationships described in the previous paragraph and in Table 4 after stratifying by maternal level of education. Compared with children of mothers with more than 12 years of education, children of mothers with 12 or fewer years of formal education had significantly lower mean values for percent predicted FVC (101.4% vs 98.2%; $P = .041$) and percent predicted FEV_1 (100.6% vs 97.2%; $P = .023$) and this effect was independent of maternal of smoking and parental symptoms. Maternal smoking (≥ 10 cigarettes per day) was associated with significantly higher levels of percent predicted FVC in girls, and this was independent of maternal education (105.9% compared with 98.0% for daughters of nonsmoking mothers; $P = .01$). There were no significant differences in percent predicted FVC between sons smoking and nonsmoking mothers (102.0% vs 100.5%; $P = .09$). The effect of maternal smoking on percent predicted $FEF_{25\%-75\%}$ was highly dependent on maternal level of education. Children of mothers who had 12 or fewer years of formal education and smoked 10 or more cigarettes per day had 15.7% lower mean values for percent predicted $FEF_{25\%-75\%}$ than children of mothers of the same level of education who were nonsmokers or smoked fewer than 10 cigarettes per day (82.8% vs 98.5%, respectively; $P < .005$). This effect was more noticeable and reached statistical significance only in boys (data not shown). Maternal smoking had no effect on percent predicted $FEF_{25\%-75\%}$ values in children of mothers who had at least some education beyond high school (98.5% vs 99.0%, respectively; $P = .9$).

DISCUSSION

In this prospective study we showed that the risk of developing asthma before age 12 was two and a half times higher in children whose mothers smoked 10 or more cigarettes per day at enrollment and had 12 or fewer years of formal education than in children of mothers of the same level of education who were nonsmokers or smoked fewer than 10 cigarettes per day. Maternal smoking had no significant effect on the incidence of asthma among children of more educated mothers. These results were independent of reported respiratory symptoms in parents. Likewise, children of less educated mothers who smoked more than 10 cigarettes per day at enrollment had 15% lower values for percent predicted $FEF_{25\%-75\%}$ (a spirometric parameter that reflects intrathoracic airway function) during follow-up compared with children of mothers of similar level of education who smoked fewer than 10 cigarettes per day or did not smoke. Maternal smoking had no significant effect on percent predicted $FEF_{25\%-75\%}$ among children of mothers with more than 12 years of education.

It is unlikely that our results may be explained by some unknown source of bias. To assess smoking habits, we used a questionnaire that was completed by parents when the child was enrolled into the study (before age 2 in 75% of the cases) and before the child's asthma had been diagnosed. Although this does not totally avoid the possibility of smoking parents' overreporting asthma in their children, it does make biases in smoking reports by parents of symptomatic children more unlikely. We had no information on the exact quitting time for ex-smokers, especially if quitting had occurred before or after the pregnancy with the child enrolled in the study. In addition, results for children of nonsmoking mothers were not different from those of children whose mothers were ex-smokers. For these reasons, we added children of mothers who were ex-smokers when the child was enrolled into the study to those of nonsmoking mothers. If any of these mothers who had quit smoking were actually smoking during the pregnancy or the child's early life, results could be biased but toward no effect.

Our group[6] and others[13] have shown that symptomatic parents may overreport respiratory symptoms in their children. Our present results, however, were independent of this possible source of bias. We chose physician-diagnosed asthma (as reported by parents) as outcome because in our population sample this variable has shown stable and meaningful relationships both with lung function parameters[14] and with indices of allergic sensitization.[15] The parallel effects of maternal smoking on cumulative incidence of asthma and on percent predicted $FEF_{25\%-75\%}$ is additional persuasive evidence against reporting bias as a possible explanation of our findings. Moreover, cumulative incidence of asthma was slightly (albeit not significantly) higher in children of more educated, nonsmoking mothers compared with children of less educated, nonsmoking mothers (Table 3). If anything, underreporting of asthma for children of less educated mothers would bias our estimate of relative risk toward no effect.

Cumulative incidence of asthma in our sample (11.5%) was higher than the frequency of asthma reported in other surveys performed in the United States, such as the Second National Health and Nutrition Examination Survey.[16] Methodologic factors may explain these differences; most reported studies are cross-sectional surveys and their main outcome variable is usually prevalence of active asthma.[16] For the purpose of that type of survey, subjects who may have had asthma in the past but who do not have asthma at the time the survey is conducted are not considered to have asthma. Our longitudinal study, vice versa, considered as having asthma any subject who had a new diagnosis of asthma and had active asthma *at any time* during follow-up. In addition, specific characteristics of our target population such as in-migration patterns[17] may also explain the higher incidence of asthma reported herein.

There are many possible factors which may explain the greater effect of maternal smoking on asthma incidence in children of mothers with 12 or fewer years of formal education. Total cigarette consump-

tion was not higher in less educated than in more educated mothers and, therefore, does not explain our findings. Crowding and worse housing conditions may increase exposure to sidestream cigarette smoke among children of less educated mothers. It could also be argued that knowledge of the possible ill effects of environmental tobacco smoke may have stimulated mothers with better education to avoid smoking when their children were present in the room. However, the great majority of the subjects of this study were enrolled in the 1970s, when there was probably much less public awareness of the health effects of passive smoking. Increased exposures to aeroallergens as well as nutritional factors may make children of less educated mothers more susceptible to environmental tobacco smoke inhalation. It is relevant to note that children of mothers with 12 or fewer years of formal education had significantly lower values for percent predicted FVC and FEV_1, but not for percent predicted $FEF_{25\%-75\%}$, and this association was independent of maternal smoking and parental respiratory symptoms. This confirms a previous report by Vedal and coworkers,[18] who showed that children of lower socioeconomic status had significantly lower mean levels of FVC and forced expiratory volume in 0.75 second ($FEV_{0.75}$) but not of $FEF_{25\%-75\%}$ than the rest of the population. Lung size may thus differ in children of different socioeconomic backgrounds. However, since FVC and FEV_1 are effort-dependent, differences in expiratory muscle strength (and probably in nutritional status) may also explain these findings. If and how these differences may alter susceptibility to environmental tobacco smoke is unknown.

The mechanisms by which maternal cigarette smoke may increase the risk for developing asthma and induce reductions in lung function in children are unknown. Maternal smoking may affect airway development,[2] and we have previously shown that diminished airway function may be a risk factor for recurrent wheezing during infancy and early childhood.[19] Parental smoking is also associated with an increased prevalence of skin test reactivity to common aeroallergens[3,20] and an enhanced bronchial responsiveness in their children,[3] and these effects may increase the risk for the development of asthma. It was recently suggested[21] that maternal smoking during pregnancy and direct postnatal tobacco smoke inhalation may have different effects on the child's lungs. We did not request information on maternal smoking during and after pregnancy, and it is often difficult to separate these effects, because most mothers do not change their smoking habits after the child's birth.[22] Animal models suggest, however, that smoking during pregnancy may alter elastin deposition and increase compliance of the lungs of the fetus.[23] Abel and co-workers[24] found that lung weight (corrected for body weight) was higher in female rats exposed to nicotine during pregnancy than in controls. Interestingly, we found that, independent of maternal education, daughters of smoking mothers had significantly larger FVC values than daughters of nonsmoking mothers. This finding confirms the report by Vedal and coworkers[18] of higher FVC levels in daughters of smoking mothers. Both a higher lung compliance and an increase in the amount of lung parenchyma may explain these findings. Decrements in $FEF_{25\%-75\%}$ paralleled the increases in asthma incidence and were thus observed only in children of smoking mothers with 12 or fewer years of formal education and were more marked in boys. In contrast, increases in FVC were observed only in girls, regardless of maternal education. This suggests that there may be different mechanisms through which maternal smoking affects lung development. Perhaps intrauterine effects are independent of socioeconomic level and may affect girls more than boys, whereas postnatal smoke exposure is a function of specific living conditions and may affect boys more than girls.[3] Further studies are needed to elucidate these issues.

Our data suggest that children of lower socioeconomic status are at increased risk of developing asthma if their mothers smoke 10 or more cigarettes per day. This finding may have important implications for our understanding of recently described changes in the epidemiology of asthma. Several reports have indicated that prevalence of asthma,[25] hospitalization rates for acute asthma,[26] and asthma mortality[27] in children and young adults increased during the period between 1975 and 1985. Data from the National Center for Health Statistics indicate that increases in morbidity and mortality rates for asthma are particularly important among minorities.[27] A recent study[27] suggested that these differences between ethnic groups are in large part attributable to socioeconomic factors. Studies on the prevalence of smoking in the United States also show that cigarette consumption increased until the mid-1970s and declined steadily since then, but until 1985, smoking initiation rates significantly increased among women with 12 or fewer years of education.[7] Our results are therefore compatible with the hypothesis that the recent increases in prevalence and severity of childhood asthma may be at least in part attributable to an increase in the prevalence of smoking among less educated mothers.

In conclusion, our results suggest that many cases of childhood asthma may be prevented through a sustained effort to discourage smoking initiation and to encourage smoking cessation, particularly among less educated women of childbearing age.

ACKNOWLEDGMENT

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ANNOUNCEMENT
1992 PEDIATRIC CARDIOLOGY EXAMINATION

The American Board of Pediatrics (ABP) will administer the certifying examination in Pediatric Cardiology on Tuesday, August 11, 1992, in three U.S. cities.

Applications will be available November 1, 1991. Registration will extend from November 1, 1991, to January 31, 1992. The application fee for the examination is $1,150, but applications postmarked after DECEMBER 31, 1991, must include an additional $200 late fee. NEW APPLICATIONS POSTMARKED AFTER JANUARY 31, 1992, CANNOT BE ACCEPTED FOR THE 1992 EXAMINATION.

Each application will be considered individually and must be acceptable to the Sub-board of Pediatric Cardiology. Please contact the ABP for eligibility requirements.

Re-registration materials will be mailed to eligible candidates on January 2, 1992. The fee is $1,050.

Please direct inquiries to:

American Board of Pediatrics
111 Silver Cedar Court
Chapel Hill, NC 27514-1651
Telephone: (919) 929-0461

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Arshad, S.H., and Hide, D.W., "Effect of Environmental Factors on the Development of Allergic Disorders in Infancy," J Allergy Clin Immunol 90(2): 235-241, 1992.

The authors assessed the possible effects of environmental factors on the development of allergic disorders in 1167 infants in this population-based prospective study. The authors reported that environmental factors such as maternal smoking, lower SES, and being born in summer appeared to be associated with the prevalence of asthma. These factors, however, did not appear to be associated with eczema or food intolerance. The authors concluded that "the environmental factors had a profound effect on the prevalence of asthma but not on other allergic disorders."

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Effect of environmental factors on the development of allergic disorders in infancy

Syed Hasan Arshad, MRCP, and David Wallace Hide, FRCP

Newport, Isle of Wight, England

A total of 1167 infants were followed for 1 year in a population-based prospective study to assess the effect of environmental factors on the development of allergic disorders. Some of these environmental factors are interdependent. Mothers who formula fed their infants smoked more often ($p < 0.001$) and tended to belong to lower social classes ($p < 0.01$). Logistic regression analysis was performed to adjust for these confounding variables. [redacted] *($p = 0.02$). Infants in lower socioeconomic groups developed asthma significantly more often ($p = 0.03$) than infants born in higher socioeconomic groups. There was a nonsignificant trend for infants born in summer to develop asthma more than infants born in winter ($p = 0.08$). No effect of these factors was observed on eczema, food intolerance, or on the subgroup of infants with definite allergy (clinical disorder with positive skin prick test [SPT]). Exposure to animal dander did not influence the prevalence of clinical disorder, but positive SPT reaction to cat dander was more prevalent in infants who were exposed to cats and/or dogs ($p = 0.04$). Positive SPT to house dust mite occurred significantly more often in infants who were formula fed ($p = 0.05$). The environmental factors had a profound effect on the prevalence of asthma but not on other allergic disorders. (J ALLERGY CLIN IMMUNOL 1992;90:235-41.)*

Key words: Environmental factors, maternal smoking, season of birth, asthma, allergic disorders

From the Clinical Allergy Research Unit, St. Mary's Hospital, Newport, Isle of Wight.
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Reprint requests: D. W. Hide, FRCP, Clinical Allergy Research Unit, St. Mary's Hospital, Newport, Isle of Wight, U.K. PO30 5TG.
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The interplay of genetic and environmental factors in the development of allergic disorders remains a subject for extensive investigation. The possibility of manipulating environmental factors to prevent the development of allergy attracts attention. Factors encountered in infancy may be of special importance.[1] Since the pioneer study of Grulee and Sanford,[2] there have been numerous studies of the protective effect

of breast-feeding with conflicting results.[3] The effect of passive smoking[4,5] and month of birth[6,7] have also been investigated. The aim of this study on infants born consecutively during a period of 14 months was to study the effect of method of feeding, passive smoking, season of birth, presence of pets, and social class on the prevalence of allergic manifestations in infancy.

Abbreviations used	
SPT:	Skin prick test
HDM:	House dust mite
S-E:	Socioeconomic
OR:	Odds ratio
CL:	Confidence limit

MATERIAL AND METHODS

The parents of 1215 infants born in the Isle of Wight between January 1989 and February 1990 were contacted soon after the birth of their child to participate in a prospective study to determine the influence of genetic and environmental factors on the development of allergic symptoms in infancy. Data on the influence of family history of atopy, cord IgE level, and pets on allergic disorders have been published separately.[8,9] The study was fully explained and informed consent was obtained. Approval for the study was given by the local ethical committee. Forty-two parents moved from the island during the first year and six families declined to attend follow-up appointment. This analysis is based on data from 1167 infants.

Family history

Information was obtained on the history of atopic disorders in the immediate family. A diagnosis of asthma, eczema, and allergic rhinitis was accepted when diagnosis had been made and treated by a doctor. The infant was regarded as having a positive family history when either parent or sibling suffered from one or more atopic disorder. Allergy in distant relatives was not considered.

Parental smoking

Information was obtained on the parental smoking habits separately for mother and father. Parents who smoked regularly (one or more cigarettes a day) were regarded as smokers. Occasional smoking (less than one cigarette per day) was disregarded.

Pets

Information was also obtained on the presence or absence of pets in the house.

All infants were observed regularly by health visitors (registered nurses with postgraduate training) up to the ageof 1 year. The health visitors recorded feeding history and details of any medical problem. Any infant with a history suggestive of allergic disorder was examined by Dr. Arshad, and SPTs were performed with allergen extracts (Soluprick, ALK Laboratories, Copenhagen, Denmark) against timothy-grass pollen, cat dander, and HDM in every infant. These three allergens were selected since >90% of atopic adults would react to one or more of these allergens. Additional SPTs were performed if the history suggested the tests. A wheal of the same size as the wheal to histamine response (1 mg/ml) was regarded as + + +, and half that size, + +. Flare alone was ignored; + + or more was considered positive. Allergic disorders were defined as follows:

Asthma: three or more separate episodes of cough and wheezing

Eczema: chronic or chronically relapsing, itchy dermatitis (lasting more than 6 weeks) with characteristic morphology (areas of scaly, erythematous, and pruritic lesions) and distribution (face, postauricular area, scalp, extensor surface of extremities, and flexural creases)

Rhinitis: recurrent nasal discharge or blockage with attacks of sneezing and itchy eyes

Food reactions: a history of vomiting, diarrhea, colic, or rash within 4 hours of ingestion of a particular food on at least two occasions

Definite allergy: one or more disorders as defined above with positive SPT

Hospital records were scrutinized on all infants who were hospitalized during the first year for additional information.

Infants breast-fed exclusively for 3 months were classified as breast-fed, and the remainder were classified as formula-fed. Information on pets and tobacco smoking within the house was updated at 1 year on all infants.

S-E class

Data on the occupation of father and mother were obtained from hospital maternity notes. The infants were classified by the father's occupation; the mother's occupation was coded if she was a single parent or if her husband was unemployed and she was employed. The social classes were formed according to the Registrar General's classification: class 1, professionals (doctors, solicitors and directors); class 2, farmers, managers, teachers, engineers, etc.; class 3, skilled workers, such as nurses and technicians; class 4, low-skilled workers, such as factory workers; class 5 (a), unskilled workers, such as laborer; and class 5 (b), unemployed.

To highlight the effect of S-E class, analysis was performed with classes 1, 2, and 3 grouped together as higher S-E group (professional and skilled workers) and classes 4 and 5 (semiskilled, unskilled, and unemployed) grouped together as lower S-E group.

Season of birth

To analyze the effect of season of birth, infants were classified into four groups according to month of birth. Infants born in December, January, and February were defined as winter births. Infants born in March, April, and May were defined as spring births. Infants born in June, July, and August defined as summer births, and infants born

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TABLE I. Effect of various environmental factors on the development of allergic disorders in infancy

	Total	Definite	Asthma	Eczema	Rhinitis	Food reactions
Method of feeding						
Formula (N = 747)	22.6	6.3	12.0*	9.9	2.9	6.3
Breast (N = 420)	22.1	6.4	6.7	11.9	3.8	8.0
Maternal smoking						
Smoking (N = 281)	27.0*	6.0	17.8†	11.4	2.8	9.3
No smoking (N = 886)	21.0	6.4	7.8	10.5	3.4	6.2
Season of birth						
Summer (N = 273)	27.1	7.7‡	14.7*	12.8	4.8‡	8.4
Winter (N = 353)	19.5	3.4	7.4	11.3	1.7	5.4
S-E Group						
Lower (N = 385)	23.4	6.5	13.5*	11.8	3.6	8.1
Higher (N = 323)	21.4	9.0	6.5	12.1	3.7	7.4
Cats and/or dogs						
Yes (N = 601)	21.6	6.2	9.0	9.3	3.0	6.5
No (N = 566)	23.3	6.5	11.5	12.4	3.5	7.6

All figures are percentages.
*$p < 0.01$.
†$p < 0.001$ (χ^2 test with Yates's correction).
‡$p < 0.05$.

in September, October, and November defined as autumn births.

Statistical methods

Chi-square test with Yate's correction was used for the detection of difference between proportions. Logistic regression analysis was used to obtain the independent contribution of factors to the risk of allergic disorders. With asthma as the dependent variable, all risk factors of interest were included in the model, and significance was tested for each one, controlling for all other factors by means of the likelihood ratio test. Adjusted ORs with 95% confidence intervals were calculated. With total and definite allergy as the dependent variable, a stepwise procedure was used to build the model with a cutoff of $p = 0.05$ used to determine entry into the model. Statistical analyses were performed with SPSS/PC+ V4 (SPSS, Inc., Chicago, Ill.).

RESULTS

The percentage of infants with allergic manifestations according to various risk factors is presented in Table I. Breast-feeding offered some protection against asthma ($p < 0.01$). Asthma was more common in infants whose mothers smoked ($p < 0.001$). Infants born in the summer months (June, July, and August) suffered from asthma more frequently ($p < 0.01$) than infants born in winter months (December, January, and February). A higher proportion of infants belonging to the lower S-E group suffered from asthma ($p < 0.01$) but not other allergic disorders. No difference in any allergic disorder could be demonstrated between children with or without pets (cats and/or dogs) at 1 year.

Three hundred forty-four infants were referred to the clinic by the health visitors, and all infants were skin tested. The percentage of infants with skin reactivity at 1 year to common inhalant and food allergens for each risk factor is presented in Table II. Reaction to HDM occurred significantly more often ($p = 0.05$) in infants who were formula-fed and in infants exposed to maternal smoking. A significantly higher proportion of infants whose mothers did not smoke demonstrated positive reaction to egg ($p = 0.05$). Reaction to cat dander was more prevalent in infants who were exposed to cats or dogs ($p = 0.05$).

Some of these environmental factors are interrelated. There were highly significant differences in smoking habit and S-E class between groups of mothers who chose to breast-feed and those who formula-fed (Table III). Moreover, in the higher S-E group, only 14% of the mothers smoked compared with 31.4% in the lower S-E group ($p < 0.001$). The prevalence of maternal asthma was similar in various subgroups (Table III). Because of these confounding variables, the net effect of the factors may not be as is outlined in Tables II and III. The logistic regression model was used to obtain the adjusted ORs for each factor. The baseline for each factor was defined as method of feeding, breast-feeding; smoking, no maternal smoking; S-E groups, higher S-E group; season of birth, winter births; pets, no cats or dogs; maternal

TABLE II. Effect of environmental factors on skin test reactivity to common inhalant and food allergens

	GP	HDM	Cat	Dog	Egg	Cow's milk	Others*
Method of feeding							
Formula (N = 222)	1.4	7.7†	5.0	1.4	9	3.2	2.7
Breast (N = 122)	2.5	0.8	4.1	1.6	9.8	5.7	3.3
Maternal smoking							
Smoking (N = 90)	1.1	10†	6.7	2.2	3.3	2.2	2.2
No smoking (N = 254)	2.0	3.5	3.9	1.2	11.4†	4.7	3.1
Season of birth							
Summer (N = 100)	2.0	5.0	5.0	1.0	7.0	4.0	5.0
Winter (N = 89)	0	4.5	4.5	1.1	6.7	2.2	1.1
S-E group							
Lower (N = 123)	0.8	5.7	2.4	1.6	8.9	1.6	4.9
Higher (N = 93)	5.4	5.4	9.7	1.1	12.9	6.5	4.3
Cats and/or dogs							
Yes (N = 165)	0.6	4.9	7.3†	1.2	8.5	4.8	3.6
No (N = 179)	2.8	5.6	2.2	1.7	10.1	3.4	2.2

GP: Grass pollen.
All figures are percentages.
*Include tree pollen, budgie, wheat, peanut, strawberry, and fish.
†$p < 0.05$ (χ^2 test with Yates's correction).

asthma, mother did not have asthma; sex, female; SPT, negative.

Unfortunately, entries of parent's occupation were incomplete in the maternity notes, and these data were available for only 708 infants. However, infants in which S-E class was known were compared with infants in which it was not known for various confounding variables (Table III). There were no significant differences.

The predominant effect of environmental factors was on the development of asthmatic symptoms. Logistic regression was performed with asthma as the dependent variable, including all factors of interest ($n = 708$). Maternal smoking, lower S-E group, maternal asthma, and male sex were significant risk factors (Table IV).

Formula-feeding and summer birth failed to reach statistical significance when they were adjusted for other confounding variables in the model. When paternal smoking was included as a separate factor, it was not significant (OR = 0.91; CL = 0.4 to 1.86) and had no effect on the significance of other factors.

When S-E group was excluded from the model so that all 1167 infants can be used, summer birth (OR, 2.13; CL, 1.25 to 3.66; $p = 0.006$) and formula-feeding (OR, 1.62; CL, 1.02 to 2.77; $p = 0.04$) became significant. The statistical significance of maternal smoking, maternal asthma, and male sex was also increased ($p < 0.001$ in each case).

Twenty-seven percent of infants with asthma had skin test positive to one or more allergens. Skin test sensitivity might have an effect on the relationship of asthma to various risk factors. To adjust for this, SPT was added to the next regression model (Table V). All data were available on 210 infants. Maternal smoking and S-E group remained significant risk factors.

The influence of risk factors on the prevalence of total allergy (infants with one or more allergic disorder) and definite allergy (subgroup with positive skin tests to one or more allergens) was analyzed with a stepwise procedure. With regard to total allergy, maternal smoking (OR, 1.64; CL, 1.10 to 2.45; $p = 0.02$) and maternal asthma (OR, 2.71; CL, 1.66 to 4.44; $p < 0.001$) were the only significant factors. Summer birth ($p = 0.06$) and sex ($p = 0.06$) just failed to reach statistical significance. Only maternal asthma was significantly related to infants with definite allergy (OR, 2.82; CL, 1.44 to 5.54; $p = 0.005$).

With positive skin test to HDM and cat as the dependent variable, logistic regression was performed to test the significance of method of feeding, maternal smoking, S-E group, month of birth, and presence of cat or dog in 344 infants in which skin tests were done. For skin test sensitivity to HDM, formula-feeding was the significant risk factor (OR, 8.04; CL, 0.98 to 67.11; $p = 0.05$). Presence of cats or dogs in the house was a risk factor for skin test sensitivity to cat dander (OR, 3.29; CL, 1.04 to 10.46; $p = 0.04$).

DISCUSSION

Allergic symptoms are extremely common during the first year of life. Symptoms do not always represent IgE-mediated type I allergy. Adverse food re-

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TABLE III. The relationship of various confounding variables to method of feeding, maternal asthma, and known/unknown social class

	Formula (N = 747)	Breast (N = 420)	Mat asthma (N = 122)	No mat asthma (N = 1045)	SC known (N = 708)	SC not known (N = 459)
Sex	357 (47.8%)	220 (52.4%)	60 (49.2%)	517 (49.5%)	338 (47.7%)	239 (52%)
Pos FH	424 (56.8%)	236 (56.2%)	—	—	390 (55%)	270 (58.8%)
Mat asthma	78 (10.4%)	44 (10.5%)	—	—	79 (11.2%)	43 (9.4%)
Smoking mothers	232 (31.1%)	49* (11.6%)	30 (24.6%)	251 (24%)	167 (23.6%)	114 (24.8%)
Lower S-E group	261 (59.5%)	124† (46.1%)	42 (53.2%)	343 (54.5%)	—	—
Formula feeding	—	—	—	—	439 (62%)	308 (67%)

Mat, Maternal: *SC*, socioeconomic class: Pos FH, positive family history of atopy.
*$p < 0.001$ (χ^2 test with Yates's correction).
†$p < 0.01$.

TABLE IV. Effect of various risk factors on the development of asthma in infancy (N = 708)

Risk factors	OR	95% CL	Significance
Formula feeding	1.65	0.91-2.99	0.09
Maternal smoking	2.30	1.34-3.92	0.003
Lower S-E group	1.84	1.05-3.20	0.03
Season of birth			
Autumn	1.33	0.56-3.17	0.52
Spring	0.83	0.35-1.94	0.66
Summer	1.97	0.91-4.25	0.08
Cats and dogs	0.69	0.42-1.17	0.16
Maternal asthma	2.45	1.29-4.78	0.01
Sex			
M	1.80	1.08-3.01	0.02

TABLE V. Effect of various risk factors on the development of asthma in infancy (after adding SPT as an independent variable; N = 210)

Risk factors	OR	95% CL	Significance
Formula feeding	1.77	0.88-3.56	0.11
Maternal smoking	2.89		0.003
Lower S-E group	2.45	1.21-4.88	0.01
Season of birth			
Autumn	0.77	0.27-2.23	0.63
Spring	0.71	0.25-2.02	0.52
Summer	1.33	0.51-3.43	0.56
Cats and dogs	0.94	0.49-1.80	0.86
Maternal asthma	1.49	0.67-3.33	0.33
Sex			
M	1.56	0.81-3.04	0.18
Positive SPT	3.20	1.55-6.58	0.002

actions, infantile eczema, and rhinitis could all have different immunologic mechanisms. A subgroup of infants with definite allergy was defined whose symptoms were backed by relevant positive SPTs. In infancy, bronchial hyperreactivity is revealed by recurrent cough and wheeze, usually after a viral respiratory tract infection. It has been termed wheezy bronchitis, infantile wheezing, pseudoasthma, or asthma. There is controversy in the literature as to the nature and outcome of recurrent wheezing in infancy.[10] A longitudinal study by Williams and McNicol[11] concluded that wheezing in response to viral infections and asthma has the same underlying basic disorder. Park et al.[12] found that 87% of infants who wheezed during the first year did not have asthma at the age of 10 years, although they were more likely to have asthma with increasing number of wheezy attacks during the first year. We preferred to use the term asthma for wheezy infants, since there was strong genetic component in this group (significant relation to maternal asthma and male sex).

This finding is not to imply that most of these infants will continue to wheeze or that they are necessarily atopic. Indeed, evidence for atopy (positive SPT) was found in only 27% of infants with recurrent wheezing during the first year.

The environmental factors studied in this cohort were method of feeding, passive smoking, social class, season of birth, and exposure to pets. The first three risk factors are closely related, and any individual effect would have to be adjusted for these and other possible variables, such as maternal asthma and

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sex of the infant. None of the environmental factors had any significant effect on eczema, rhinitis, or food intolerance (Table I). The effect on "total allergy" was primarily due to the effect on prevalence of asthma.

In line with several previous studies,[13-15] we could not detect an association between mode of feeding and incidence of total allergy. Some studies have found a protective effect of breast-feeding on wheezing.[16, 17] Since there are so many interrelated confounding variables, these must be taken into account when the effect of method of feeding on the development of allergic disorders is being assessed. In this study, there appeared to be a protective effect of breast-feeding against wheezing episodes, but when adjustment was made for other variables, this effect became nonsignificant. It is believed that breast-feeding provides immunologic protection against infections with transfer of IgA and IgG through breast milk. If infantile wheezing is a nonspecific response to viral infections, it was surprising that no significant effect of breast-feeding was observed. There was an association between sensitivity to HDM and formula-feeding. No firm conclusions could be drawn on the relationship to skin test sensitivity because the only infants who were skin tested were infants who demonstrated symptoms and who had been referred to the clinic by health visitors. This possible association needs confirmation.

Passive smoking is known to increase bronchial responsiveness and symptoms in children with asthma.[18] Parental smoking, particularly maternal smoking, increases the risk of respiratory illness during the first year of life.[19-21] [redacted] Paternal smoking was not a risk factor, presumably because the father does not usually smoke in the vicinity of the infant for sufficiently long periods. It is unlikely that parents misled us about their smoking habits since information on smoking, as well as the presence of pets, was checked by the health visitors who visit homes frequently after the birth of a baby.

Recently, Murray and Morrison[22] reported that children with atopic dermatitis are at a greater risk of developing asthma if the mother smokes. It was believed that atopic dermatitis signified a predisposition to atopy, whereas smoking acts as an adjuvant factor. In this cohort, the effect of maternal smoking was independent of hereditary factors, such as maternal asthma or sex of the infant and skin test sensitivity of the infant. From these data, maternal smoking appears to be a risk factor for wheezy illness but not for atopy. This finding was confirmed when these data were analyzed for the subgroup of infants with definite allergy. None of the environmental risk factors were significant for this group of infants.

We combined data for S-E classes 1, 2, and 3 because the number for classes 1 and 2 was small and they were similar in manner. Classes 4 and 5 were also combined for the same reason. There was an independent effect of S-E class on asthmatic symptoms. It was probably an indirect effect through bad housing conditions, such as dampness and crowding with increase risk of transmissible respiratory infections. Other studies have found a relationship between S-E class and wheezing during infancy.[16, 23]

There was a trend for respiratory symptoms to be more prevalent in infants born in summer months, but no significant independent effect could be demonstrated on either asthmatic symptoms or skin test sensitivity to grass pollen or HDM. Morrison Smith and Springett[7] found a higher risk of asthma and positive skin reactions to HDM for infants born in summer months. The cause of this relationship remains unclear. Virus infections are more common in winter; therefore, this cannot explain an increased incidence of respiratory symptoms. Exposure to birch pollen in the first few months of life was believed to increase the risk of birch-pollen allergy.[24] Further studies are needed to clarify the association between month of birth and allergic sensitization.

Environmental factors play an important role in the prevalence of recurrent wheezing but not other allergic disorders in the first year of life. Exposure to some environmental factors in early life may be important in increasing the risk of sensitization. Unfortunately, there appears to be a clustering of avoidable risk factors. Mothers who formula-fed their babies tended to smoke and more often belonged to lower S-E groups. It is important to educate mothers, especially mothers belonging to lower S-E groups, to breast-feed and avoid smoking.

We thank health visitors and midwives of the Isle of Wight Health Authority for their help and cooperation. Mrs. Fiona Lampe, Statistical Department, Southampton University, for help with statistical analysis, and the Isle of Wight Health Authority Trustees and Wessex Medical Trust for their generous support.

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Soferman, R., Greif, J., Kivity, S., and Topilsky, M., "Prognostic Factors in Childhood Asthma -- A 10-Year Follow-Up Study," Allergy Suppl 47(12): 8, 1992.

The abstract of this study reports that 92 adults aged 15-25 years who had moderate to severe asthma during childhood underwent reevaluation of their clinical status and pulmonary function tests ten years after diagnosis. The authors report that age of onset, breast feeding, parental atopy, parental smoking, socioeconomic condition, treatment with DSCG, serum IgE level, and routine skin tests and pulmonary function tests were not statistically significant.

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Allergy, 47(S12):8, 1992

AN OBJECTIVE ASSESSMENT OF ENVIRONMENTAL TOBACCO SMOKE (ETS) EXPOSURE IN 5-7 YEAR OLD CHILDREN.

T. Assadullahi, S. Clark, J.O. Warner.
University Department of Child Health, Southampton General Hospital, Southampton SO9 4XY

ETS has been associated with increased frequency of raised IgE and eczema in infancy, but this has not been quantitated accurately by measuring levels of exposure and correlating them with the frequency and severity of the conditions. Exposure to ETS is measured using cotinine, the major metabolite of nicotine which has a half life of 20 hours and is widely considered the analyte of choice. We have developed a sensitive assay of cotinine using high performance liquid chromatography (HPLC) to quantitate ETC exposure in a group of 5-7 year old asthmatic children compared to a group of age matched controls. We chose to use mixed unstimulated saliva collected by absorbtion into dental rolls in the mouth for 5 minutes. Our modified extraction procedure was highly reproducible with a 96% retrieval rate of cotinine from spiked saliva. The parents were asked to fill in a questionnaire on atmospheric pollutants to obtain an estimate of declared ETS exposure in the home. Results showed 31% of the asthmatic patients according to the parents were exposed to ETS but by HPLC 68% had been so exposed (n=19). From the control group the figures were 40% and 51% of patients respectively. Therefore an objective assessment is essential as ETS is more ubiquitous than is apparent from questionnaire alone. Large studies are required to establish associations between ETS exposure and atopic disease.

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PROGNOSTIC FACTORS IN CHILDHOOD ASTHMA - A 10-YEAR FOLLOW-UP STUDY

R. Soferman, J. Greif, S. Kivity, M. Topilsky, Institute of Pulmonary and Allergic Diseases, Tel-Aviv Sourasky Medical Center, Israel.

92 adults aged 15-25 years, who had moderate-to-severe asthma during childhood, underwent reevaluation of their clinical status and pulmonary function tests 10 years after diagnosis. Four classes of asthma severity were established. The factors predicting the outcome of childhood asthma were studied according to this classification. The following factors were not found to be statistically significant: age of onset ($p<0.07$), breast feeding ($p<0.09$), parental atopy ($p<0.7$, $p<0.4$), parental smoking habits ($p<0.7$, $p<0.2$), socioeconomic condition ($p<0.4$), treatment with D.S.C.G. ($p<0.08$), serum IgE level ($p<0.4$), routine skin tests and pulmonary function tests. Early treatment with beclomethasone for at least 2 years correlated significantly with improvement ($p<0.03$); being the eldest son and positive skin test to olive tree pollen correlated significantly with asthma deterioration ($p<0.05$, $p<0.05$).

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Wood, P.R., Hidalgo, H.A., Prihoda, T.J., and Kromer, M.E., "Hispanic Children with Asthma: Morbidity," Pediatrics 91(1): 62-69, 1993.

The authors identified children with asthma from a registry of all patients aged 6 to 16 years of age who received emergency care or were hospitalized for asthma in the facilities of the Bexar County Hospital District between November 1988 and November 1989. Information was obtained from parents by a trained interviewer. The children also were interviewed. FVC maneuvers were performed on the children at scheduled visits. The authors report that the child's asthma had a larger "total impact" on the family if there was a smoker in the household. The authors conclude that "two factors, knowledge about asthma and exposure to cigarette smoke in the home, were significantly associated with outcome in these children and therefore should be addressed in interventions."

Hispanic Children With Asthma: Morbidity

Pamela R. Wood, MD*; Humberto A. Hidalgo, MD*; Thomas J. Prihoda, PhD‡; and Megan E. Kromer, PhD

ABSTRACT. Hispanic children represent a large and growing segment of the poor and disadvantaged children in our country. Asthma and other chronic respiratory diseases have a significant impact on poor children. Yet there are few descriptions of the specific morbidities and barriers to health that Hispanic children with asthma encounter, and data on predictors of morbidity among these children are unavailable. The purpose of this study is to describe the morbidity associated with asthma in Hispanic children and to identify factors that predict morbidity. A group of Hispanic children with moderate asthma followed in the clinics of the University of Texas Health Science Center at San Antonio were studied. Children aged 6 to 16 years with at least two acute-care visits or one hospitalization for asthma during the previous year were enrolled. Data sources included standardized questionnaires, spirometry, medical records, and school attendance records. Seventy-eight Hispanic children were enrolled in the study (mean age = 9.4 ± 2.7 [SD]; 62% male). Fifty-two (67%) of children had been hospitalized previously. The other morbidity variables (mean ± SD) were number of days/week impaired (1.1 ± 1.2), number of days absent from school per year (13 ± 9.6), number of acute-care visits per year (3.3 ± 2.4), and number of hospital admissions per year (0.6 ± 0.8). The mean forced expiratory volume in 1 second/forced vital capacity was 79.3% (±9.1) and the mean forced expiratory flow, mid-expiratory phase, percent predicted was 69.9% (±25.1). Thirty-four children (44%) were exposed to cigarette smoke in the home. Parents answered an average of 86% (±12%) of questions about asthma correctly, but they made more errors in answering medication questions. Mean Impact-on-Family score was high (45.6 ± 6.4). Multiple regression analysis showed that Total Impact-on-Family scores were significantly increased if there was a smoker in the household and decreased when knowledge about asthma was high. Spirometry results (n = 45) did not predict any of the morbidity variables. This study identifies two factors associated with morbidity in Hispanic children with asthma that must be addressed in an intervention program: knowledge about asthma and parental smoking in the home. *Pediatrics* 1993;91:62–69; *asthma, morbidity, Hispanic American, Mexican-American, respiratory function tests, health services research, health behavior, smoking.*

ABBREVIATIONS. FVC, forced vital capacity; ATS, American Thoracic Society; FEV_1, forced expiratory volume in 1 second; FSIIR, Functional Status Measure; $FEF_{25\%-75\%}$, forced expiratory flow, mid-expiratory phase.

From the *Department of Pediatrics, ‡Department of Pathology, and §Department of Educational Resources, the University of Texas Health Science Center at San Antonio.

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Reprint requests to (P.R.W.) Dept of Pediatrics, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Dr, San Antonio, TX 78284-7808.

PEDIATRICS (ISSN 0031 4005).

Asthma is a significant health problem that affects 7% of children aged 3 to 17 years and results in 28 million disability days per year for children younger than 17 years of age.[1,2] Childhood asthma is a major reason for health service utilization, resulting in more than 3.4 million patient visits and 149000 hospitalizations per year.[3,4] Asthma is a costly disease for children and their families. One study found that an average of 6.4% of yearly family income was spent in caring for a child's asthma and that low-income families spent more than 10% of their yearly family income for the same.[5] The illness of a child with asthma also has a substantial effect on the family's activities and future plans.[6] School absenteeism is high. Children with asthma miss an average of 8.4% of school days, a significant increase over their nonasthmatic classmates.[7]

Despite abundant information about asthma in general, little is known about this disease in Hispanics. The prevalence of asthma in this population is comparable to that in non-Hispanic whites (Anglos).[8,9] However, the morbidity of asthma among Hispanic children may be greater because of poverty, lack of insurance, cultural and language barriers, and health beliefs.

Children in the lower socioeconomic classes, which include many Hispanic children, experience an excess of severe asthma and a greater degree of functional morbidity.[6] Hispanic patients have lower rates of health insurance than patients from other racial and ethnic groups.[10] They also experience cultural and language barriers to health care.[11,12] Parents of asthmatic Mexican-American children are less likely than non-Hispanic white parents to believe that their child has asthma and are more likely to use emergency department services as a primary source of care.[13]

The objectives of this cross-sectional study were to (1) describe the morbidity present in Hispanic children with asthma; (2) describe the knowledge, health practices, and perceived barriers to health care of these children and their families; and (3) identify factors that predict morbidity. This study is important because it provides detailed information about the needs and health status of a group of Hispanic children with asthma and identifies potential areas for intervention.

METHODS

Study Population

Children with asthma were identified from a registry of all patients 6 to 16 years of age who received emergency care or were hospitalized for asthma in the facilities of the Bexar County Hospital District between November 1988 and November 1989. This registry was created by reviewing written logs of emergency de-

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partment and acute-care facilities and hospital discharge records for a diagnosis of "asthma" or "reactive airway disease." The Bexar County Hospital District facilities are the major clinical sites for the University of Texas Health Science Center at San Antonio and serve a population that is 80% Mexican-American. Pediatric patients receive care from pediatric residents, other rotating residents (family practice and psychiatry), and medical students under the supervision of pediatric faculty members. These patients are mostly urban, indigent, and pay for medications and medical care on a sliding-fee scale.

Children eligible for this study had physician-documented asthma as defined by the American Thoracic Society[14] (ie, several previous episodes of airway obstruction, demonstrated clinical response to bronchodilators, and no other known pulmonary disease). Eligible children had at least two acute-care visits or one hospitalization for asthma during the year covered by the registry. Eligible children were contacted by telephone, by letter, and by personal invitation at the time of any scheduled outpatient visit. An attempt was made to enroll all children who met the eligibility criteria. All medical records were reviewed by a single registered nurse trained by the principal investigator (P.R.W.). Chart review data were used to compare study participants to "nonenrollees" and to patients who refused enrollment ("refusals").

Ethnic group membership was defined by self-identification using the US Census identifier[15] or, in the case of nonenrollees, by medical record data. The results reported here are limited to Hispanic participants. This study was approved by the Institutional Review Board of the University of Texas Health Science Center at San Antonio.

Procedure

After obtaining the parent's informed consent, a bilingual interviewer obtained information from the parent accompanying the child. Interviews were conducted in either Spanish or English, according to the parent's preference. The parent interview took approximately 45 minutes. Children were interviewed by a bilingual research nurse in a separate room. A single children's version in English of the Asthma Questionnaire was used. The child interview took 10 to 15 minutes. The interviewer and the research nurse were trained by the principal investigator, who periodically monitored interviews. Additional data were obtained by review of school attendance records and medical records. Medical visits were counted as acute-care visits for asthma only if the child received medical treatment (usually nebulized albuterol).

Spirometry

Forced vital capacity (FVC) maneuvers were performed on all children during scheduled visits. Spirometry was not done if the child had experienced an acute exacerbation of asthma requiring treatment by a physician in the previous 2 weeks. No attempt was made to control for bronchodilator use before spirometry. All measurements were made with a dry rolling seal spirometer (S & M Instruments, Doylestown, PA). Spirometric results were included in the analyses if a child completed three FVC maneuvers that met the acceptability criteria of the American Thoracic Society (ATS).[16] The FVC measurement with the largest sum of FVC and forced expiratory volume in 1 second (FEV_1) was converted to body temperature pressure standard and used for analysis. The percent of predicted spirometric variable values for gender and height were calculated using the equations for Mexican-American children reported by Hsu et al.[17]

Questionnaires

The Asthma Questionnaire is a 50-item instrument developed by the investigators. It asks specific questions regarding knowledge and beliefs about asthma and medications, health behaviors, patterns of health care, morbidity, and sociodemographic information. The children's version of the Asthma Questionnaire is a shorter instrument, which parallels the parent questionnaire. A Spanish-language version of the Asthma Questionnaire (parent version) was developed using translation and back-translation by local bilingual personnel. Deyo and coworkers' four-item language-based acculturation scale, which has been shown to be valid and reliable in a similar population, was used to measure acculturation.[18]

The Functional Status Measure (FSIIR) is a 14-item instrument that measures the child's capacity to perform age-appropriate tasks in a variety of areas. The "illness score," which measures the child's level of functioning as it relates to the child's illness, was used in the analyses. Both Spanish and English versions have been shown to be reliable and valid in other studies.[19-21]

The Impact-on-Family Scale consists of 27 items that assess the impact of the child's illness on several dimensions of family functioning. Both Spanish and English versions have been shown to be reliable in previous studies.[20-22] The Total Impact score was used in the analyses.

All Spanish-language instruments were pretested and minor changes in wording were made to adapt to local language use.

Scales and Indices

Scales were developed for each of the following constructs: morbidity, personal and family history of asthma, child's health behaviors (self-report), child's health behaviors (parent's report), and barriers to health care. For these constructs, scale scores were computed using summed responses from more than one questionnaire item. Items that decreased reliability were dropped from the scale. For example, the following 13 variables were combined to form the morbidity scale: previous hospitalization, "severe episode," current steroids, perceived severity, health compared to others, ability to play, number of days impaired per week, number of days absent per year, number of acute-care visits per year, and the four variables in Table 1. These variables were selected from an original list of 26 items.

Acculturation score, parental educational level, and income (household income/number of household members) were summed to give a sociocultural-economic status index. Finally, four indices were developed: knowledge of asthma, knowledge of prescribed medications, compliance, and avoidance of asthma triggers. For each index, component items were totaled and indexed from 0 to 1 to measure the proportion of desirable responses for each subject.

Statistical Methods

Data are given with the standard deviation unless otherwise noted. Categorical data for enrollees were compared with those of "nonenrollees" and "refusals" using χ^2.[23] Numeric variables were analyzed using one-way analysis of variance with post hoc, two-tailed Dunnett's multiple comparison test, after checking residuals for normality and influence.[24,25]

Simple bivariate relationships are described with χ^2 contingency tables for categorical measures. Parent and child questionnaire results were analyzed with the applicable choice of paired t test, Satterthwaite approximate t test, Wilcoxon signed-rank test, or κ statistic for agreement.[26] The outcome variables of morbidity score, illness score,[19] total Impact-on-Family score,[20] number of school days missed, number of acute-care visits per year, and number of days per week impaired were individually regressed on multiple predictor variables with backward elimination. The predictor variables were the following: history, sociocultural-economic status, child's health behaviors (self-report), child's health behaviors (parent's report), avoidance of asthma triggers, barriers to health care, knowledge of asthma, knowledge of prescribed medication, medication compliance, age, gender, FEV_1/FVC, and forced expiratory flow, mid-expiratory phase ($FEF_{25-75\%}$).

The final set of predictor variables significant at $P \leq .10$ from the multiple regression were subsequently analyzed as a reduced set of predictors. This allowed verification of the prediction equation with a slightly larger sample size. The final regression equations include variables significant at the .05 level. With 45 subjects there is at least a .94 power for detecting correlations as small as .50.

TABLE 1. Morbidity* (n = 78)

Variable	Mean	SD	Range
No. of hospital admissions per year	0.6	(±0.8)	(0–3)
No. of days hospitalized per year	1.3	(±2.7)	(0–14)
No. of asthma medications	2.8	(±1.4)	(0–6)
No. of days oral steroids per year	7.7	(±9.6)	(0–38)

* The Morbidity Scale (13 items) consisted of number of days impaired per week, number of days absent per year, number of acute-care visits per year, the four variables listed above, and the following six categorical variables: ever hospitalized for asthma, "severe episode" (intensive care unit admission, loss of consciousness, seizure), current steroids, perceived severity, health compared to others, and ability to play. Reliability (Cronbach's α) = .56.

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RESULTS

Study Population

One hundred seventy-five children were eligible to participate in the study, and their parents were called a mean of 1.7 times ($\pm$1.95; range: 0 to 9) by telephone. Letters were sent to the 35 (21%) families who had a disconnected telephone number. Of those contacted, 9 children refused to participate in the study ("refusals"), and 78 children were enrolled. Eighty-eight other children qualified for the study but were not enrolled ("nonenrollees"), because we were unable to contact them by telephone, by mail, or at the time of any scheduled outpatient visit. Based on chart review data, enrollees differed from "nonenrollees" in that the enrollees were older (9.9 $\pm$ 2.7 vs 8.7 $\pm$ 2.5, $P < .05$) and had more acute-care visits (3.3 $\pm$ 2.4 vs 2.2 $\pm$ 2.1, $P < .05$). Twenty-one enrollees (27%) compared with 5 nonenrollees (6%) had visited the allergy clinic at least once in the past year ($P = .001$). Forty-five enrollees (58%) compared with 22 nonenrollees (24%) had at least one visit to the pediatric residents' continuity clinic in the past year ($P < .001$). Enrollees had more total scheduled appointments in the past year than nonenrollees (1.4 $\pm$ 0.1 vs 0.5 $\pm$ 0.1, $P < .001$). Children who refused to participate were older than enrollees (12.5 $\pm$ 2.3 vs 9.9 $\pm$ 2.7, $P < .05$) and were hospitalized more days per year (4.1 $\pm$ 5.2 vs 1.2 $\pm$ 2.5, $P < .05$).

Forty-eight (62%) of 78 children enrolled were male; mean age was 9.4 ($\pm$ 2.7) years (range: 6 through 16). The families of these children were poor and the majority of parents (62%) had not completed high school. Sixty-three families (81%) had an annual household income of $12000 or less. Fifty-five (71%) children had no health insurance and only 11 (14%) had Medicaid. Most children (78%) lived in two-parent households. Sixty-six households (85%) had four or more members. Seventy-five (97%) mothers and 72 (94%) fathers considered themselves to be Mexican-American. The remaining parents were Puerto Rican (3), Cuban (1), and other Hispanics (3). Seventy respondents (91%) were the child's mother, five were the father, and two were the maternal grandmother.

Thirty-one (40%) parents chose to answer questions in Spanish. Figure 1 shows the responses to the four items of the language-based acculturation scale. The mean score on this scale was 2.3 ($\pm$ 1.2; range: 0 to 4; Cronbach's α = .65), indicating that language-based acculturation was midway between English-only language use (a score of 4) and Spanish-only language use (a score of 0).

Medications

Almost all children took medications daily for asthma. The average number of medications that these children received for asthma was 2.8 ($\pm$ 1.4; range: 0 to 6). Sixty-two children (79.5%) used aerosolized albuterol, 41 (52.6%) used theophylline, 31 (39.7%) used topical cromolyn, and 5 (6.4%) used topical corticosteroids, alone or in combination with other medications. Thirty-six children (46%) used any anti-inflammatory medication (cromolyn, topical steroids, or oral corticosteroids).

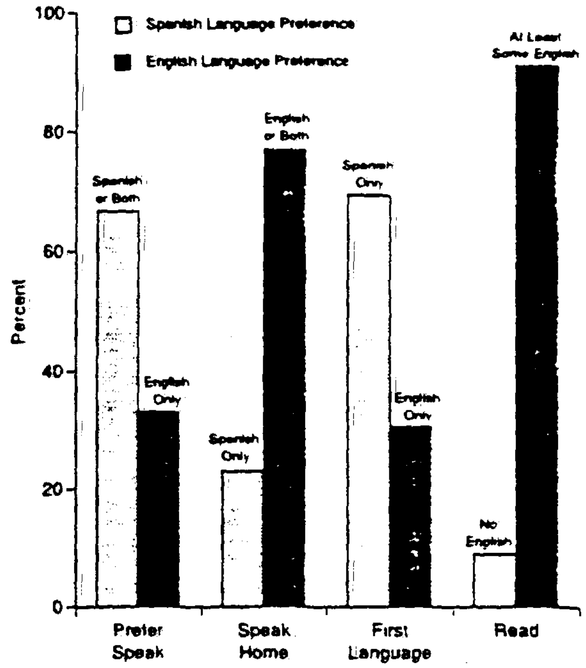

Fig 1. Language Use.

Spirometry

A trained bilingual research nurse attempted to perform spirometry on 76 children. Two children were excluded because they had experienced an acute exacerbation within the previous 2 weeks. Sixty-five children (83%) produced at least one acceptable maneuver, but only 45 (58%) had three or more maneuvers that met ATS criteria for valid analysis.[16] The spirometric data of these 45 children demonstrated mild to moderate airway obstruction, with a wide range of observed values (Fig 2). The $FEF_{25\%-75\%}$ of the children who completed three or more acceptable measurements was significantly lower than the $FEF_{25\%-75\%}$ of the children with fewer than three acceptable measurements (69.9% $\pm$ 25.1 vs 86% $\pm$ 22.9; $P = .0001$). The FEV_1, FEV_1/FVC, and peak expiratory flow rate did not differ significantly between the two groups.

Morbidity

The rate of previous hospitalization (ever) for asthma was 67% (52/78). Twenty-six children (3 3%) had been admitted to an intensive care un three had experienced loss of consciousness, one had had a hypoxic seizure, but none had been intubated because of asthma. Eleven children (14%) were taking oral or topical corticosteroids at the time of the interview. Seventy-two parents (92%) stated that their child's asthma was somewhat serious (64%) or very serious (28%). Thirty parents (39%) thought that their child's health was not as good as other children's health. Fifty-eight (74%) of the children expe enced at least occasional limitation in their ability run and play.

Children experienced a mean of 1.1 ($\pm$ 1.2; range: 0 to 7) days of impairment per week, ie, days during which their sleep was disrupted by asthma symptoms or during which they were unable to participate

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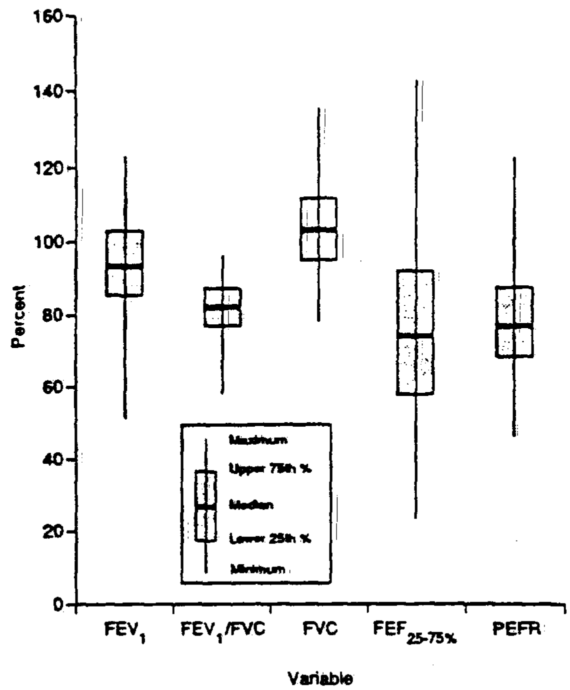

Fig 2. Spirometry (n = 45). FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; $FEF_{25-75\%}$, forced expiratory flow, mid-expiratory phase; PEFR, peak expiratory flow rate.

fully in usual activities (Fig 3, A). They were absent from school an average of 13 days (±9.6, range: 0 to 51) in the previous year. This represents 7.4% of the 175 required days of school. Sixteen children (21%) missed 2 to 3 weeks of school and 25 (33%) missed 3 or more weeks of school (Fig 3, B). Children had an average of 3.3 (±2.4; range: 0 to 12) acute-care visits for asthma during the previous year (Fig 3, C). Other morbidity variables are shown in Table 1. Cronbach's α for the morbidity scale (13 variables) was .56, with each item correlating .3 or higher with the total.

Barriers to Health Care

Ten (13%) children had no regular source of health care; they received routine care for asthma in the walk-in clinic or emergency department. Families of children with asthma experienced a mean of 2.14 (±1.35; range: 0 to 4; reliability = .64) out of 4 potential barriers to health care for their child with asthma. The most frequently mentioned barrier was paying for medications (Table 2). This was not surprising, because few children had Medicaid or insurance and because families were billed for medications from the Bexar County Hospital District pharmacy on a sliding-scale basis. Cronbach's α for the barriers scale was .64.

Health Behaviors and Attitudes

Table 3 contrasts the health behavior data from the parent's and child's versions of the questionnaire. Agreement between the answers of parents and children for some asthma care-related behaviors was modest (κ: .19 to .31). Thirty-two parents (42%) stated that they, and not their child, were the first to notice asthma symptoms. After listing their child's specific asthma triggers, parents reported that their children avoided a mean of half (0.50) of these triggers. Children reported significantly greater (0.73) avoidance of triggers. Parents reported significantly greater medication compliance than did their children. Parents reported a mean compliance of 0.89 on an index with a potential range of 0 ("never taken") to 1 ("always taken"), while their children reported a mean compliance of 0.75.

Thirty-four children (44%) were exposed to cigarette smoke in the home. Twenty-five (41%) fathers and 14 (18%) mothers living in the home were smokers. Forty-eight (62%) parents identified cigarette smoke as a trigger for their child's asthma. Twenty-four (71%) of the 34 families with a smoker in the home identified cigarette smoke as a trigger for their child's asthma.

Twenty-five (32%) parents had tried home remedies or over-the-counter medications to treat their child's asthma. The most common remedies were teas (16), cough syrups (4), and Primatene (5). However, only one parent believed that these remedies worked better than prescription medications for asthma. Three parents were unsure whether home remedies worked better. When asked to list actions taken when their child experienced an acute exacerbation of asthma, 65 parents (83%) mentioned giving asthma medications. Other commonly mentioned ac-

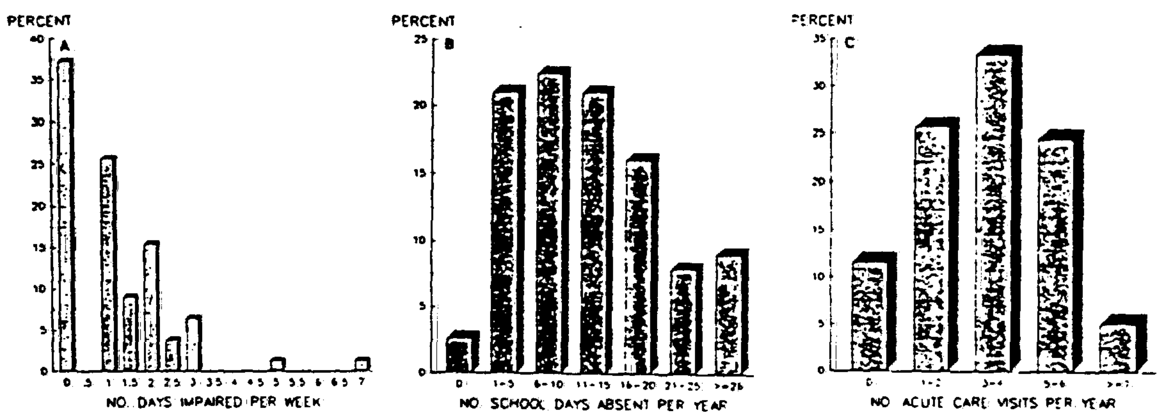

Fig 3. Frequency distribution of number of days of impairment per week (A; n = 78), number of school days absent during the past year (B; n = 76), and number of acute-care visits for asthma during the past year (C; n = 78).

TABLE 2. Barriers to Health Care (n = 78)

Variable	No. (%) Reporting
No regular source of health care	10 (13)
Payment for medications*	57 (73)
Payment for visits*	45 (58)
Time of visit*	38 (49)
Transportation*	27 (35)
Giving medications in school	14 (18)

* Items included in barriers scale (reliability = .64).

TABLE 3. Reported Health Behaviors (n = 78)

Behavior	Parent	Child	κ	P Value
Child takes medications on own some or all*	66%	56%	.32	.002‡
Who notices asthma first: child, or parent and child*	56%	45%	.06	.289‡
Do anything to remember medications†	8%	12%	.19	.049‡
Avoid known triggers (index)†	.50	.73		.0003§
Compliance (index)	.89	.78		.001§

* Items included in Child's Health Behaviors (parent's report) scale.
† Items included in Child's Health Behaviors (self-report) scale.
‡ Significance level for agreement between parent and child responses, using κ statistic and one-tailed P value.
§ Significance level for differences between parent and child responses, using Wilcoxon's signed-rank test.

tions were taking the child to the doctor (78%) and calming the child (13%).

Twenty-six respondents (33%) had received advice about treating asthma from someone other than a physician. The advisor was usually a relative or friend. However, only eight (31%) of those who had received advice found it helpful.

Knowledge

The level of knowledge about asthma in this population was high. Parents answered an average of 86% (±12%) of 11 questions about asthma correctly. Children answered an average of 69% (±21%) of 11 questions correctly. Knowledge about asthma medications was also high. The most common errors were in frequency of administration. The only significant difference between parents' and children's knowledge about medications was in knowing the name of the medication. Children were often able to describe their medications but could not state the correct name. Parent and child responses are contrasted in Table 4.

Functional Status and Impact on Family

Functional Status scores (FSIIR) showed some impairment in functioning. The mean "Illness score" was 24.2 (86%) out of a possible perfect score of 28 for a child who is not impaired by illness (Cronbach's α = .84). The most frequently endorsed impairment due to asthma was "seems to feel sick and tired." Many parents also stated that their child "acts moody" and "seems unusually irritable or cross," but they were less likely to attribute these behaviors to their child's illness. Impact-on-Family scores indicated a moderate impact of the child's illness on the family. The mean raw Impact-on-Family score was 45.6 out of a potential maximum score of 76 (Cronbach's α = .86). Many parents agreed with the following statements: "The illness is causing financial problems for the family" (58%) and "Additional income is needed to cover medical expenses" (69%). Childhood asthma also resulted in disruption of family activities and plans. Parents frequently agreed with these statements: "We have to change plans about going out at the last minute" (55%) and "Sometimes I feel like we live on a roller coaster" (80%). Data for FSIIR and Impact-on-Family are shown in Table 5.

TABLE 4. Knowledge About Asthma and Medications (n = 78)

Variable	Mean % Correct Responses		P Value*
	Parent	Child	
Asthma knowledge	86	69	.0001
Medication knowledge			
Name correct	79	55	.0001
Dose correct	69	65	.46
Frequency correct	59	51	.08

* Significance level for differences between parent and child responses, using Wilcoxon's signed-rank test.

Regression Analysis

For multiple regression, each of the significant predictor variables has an effect that is independent of the others. With the full set of predictors, including $FEF_{25\%-75\%}$ and FEV_1/FVC, backward elimination yielded no significant predictors of morbidity score, number of days absent from school, number of acute care visits per year, or illness score (FSIIR). The number of days with impairment per week was significantly predicted by history score (personal and family history of asthma and allergic disease). Total Impact-on-Family score was significantly higher if there was a smoker in the household and was lower when knowledge about asthma was high (Table 6).

DISCUSSION

This study documents the burden that asthma of moderate severity places on some Hispanic children and their families. We are aware that the results of this single study require replication and that several methodological issues need to be addressed before the results can be interpreted. First, this study was cross-sectional and was performed at a single site. The findings from this group of Mexican-American subjects may not apply to other groups of Hispanic children. Data from the Hispanic Health and Nutrition Examination Survey suggest that asthma may be more common and more severe in Puerto Rican children.[9] Whether this is due to actual differences be-

TABLE 5. Questionnaire Scores (n = 78)

Variable	Mean	SD	Range	Reliability*
Functional Status†				
Total Score	21.7	3.8	12–27	.76
Illness Score	24.2	3.9	14–28	.84
Impact-on-Family‡				
Total Impact	45.6	6.4	20–64	.86

* Measured by Cronbach's α.
† Functional Status (FSIIR) raw scores. Potential range = 0 to 28. Higher scores indicate better functional status.
‡ Total Impact score. Potential range of scores = 19 to 76. Higher scores indicate greater impact of the illness on the family.

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TABLE 6. Linear Regression Analyses (n = 45)*

No. d/wk impaired = −0.27 + 0.17 (history)
(R^2 = .22) (P = .0011)
Total impact = 61.08 + 4.09 (smoke) − 19.78 (knowledge)
(R^2 = .19) (P = .0315) (P = .0110)

* ...tory, personal and family history of asthma; smoke, smoker in ...hold; knowledge, knowledge of asthma (index).

...tween ethnic groups, to differences in living conditions (eg, urban vs rural), or to other factors is not known. Our enrollees were generally low-income patients who received care in a publicly funded health care system. Some of our findings may be attributable to problems associated with poverty. However, the socio cultural-economic status index was not a significant predictor of any of the outcomes in our ...ly. Moreover, the morbidity experienced by our ...ollees was quite similar to that reported previously for children from a broader range of socioeconomic levels.

Second, inasmuch as enrollment was limited to children who had experienced several acute-care visits or a hospitalization in the previous year, the findings cannot be generalized to other children with less severe illness. Representative community-based, cross-sectional surveys such as the Hispanic Health ...d Nutrition Examination Survey and the Child ...lth Supplement to the National Health Interview ...rvey are more appropriate sources of information about children with mild asthma. However, our enrollees represent a group of children who are important to study because their illness is a significant burden for the children and results in frequent utilization of emergency department and hospital services.

Third, although families were quite willing to participate if contacted, many families could not be con...ted. Nonenrollees had fewer acute-care visits and ...ver scheduled clinic visits. They may have been less sick than enrollees or they may have used health care facilities less frequently. Unfortunately, our data do not allow us to characterize this group further. The great difficulty that we had in contacting children with asthma who had received medical care in the previous year may also point to problems that low-income families have in accessing health care.

The rate (58%) at which children in this study com...eted FVC maneuvers that met current ATS crite...[16] deserves further comment because it is lower than the 86% rate (three acceptable FVC maneuvers in seven attempts) reported by Hsu et al[1] in normal 8- to 9-year-old children. There are several potential explanations for this difference. First are technical problems arising from the personnel who performed the spirometry or from the equipment. We believe this is an unlikely source of error because both personnel and equipment met the criteria put forth by the ATS.[16,27] A second possibility is that the rate was ...wered by the inclusion of a significant number of ...ounger children in our study (15% were younger than 7 years). Finally, the current criteria for acceptability and interpretation of FVC maneuvers may be difficult to meet for children with asthma. To our knowledge, these criteria have not been tested in groups of children of any age with lung disease.

Finally, the small sample size and relatively low reliability of some of the scales may have contributed to the small effects seen in the regression equations. We need to develop more specific measures of health behaviors, knowledge, barriers to health care, and morbidity.

As a group, our patients met the criteria for asthma of moderate severity proposed by the Expert Panel of the National Asthma Education Program[28] and were demographically similar to other groups of urban Hispanic children.[15] These children experienced significant impairment in many areas of their daily lives, and the financial and personal cost of this disease was high. Certain health behaviors, barriers to health care, and prescribing practices were identified as potential targets for intervention.

Despite relatively low rates of hospitalization, these children experienced a high impact of asthma on their daily lives as measured by school absenteeism, days with impairment, exercise limitation, and acute-care visits. The rate of school absenteeism (13 of 175 days; 7.4% of total days) was similar to that reported by Parcel et al.[7] Other authors, using data from the 1988 Child Health Supplement to the National Health Interview Survey, have shown that children with asthma miss approximately twice as many school days as children without asthma.[29] The Child Health Supplement data and the study by Parcel et al.[7] included a cross-section of children from different socioeconomic groups who had asthma of varying severity. Their data and ours indicate a substantial effect of asthma on school attendance.

Functional status scores (FSIIR) and Impact-on-Family scores were similar to values reported in other studies of chronically ill children and demonstrate the impact of asthma on the daily activities of children and their families.[19,20] In a study of inner-city, low- and middle-income children, Stein and Jessop[19] found that chronically ill children had lower functional status scores and more variation in scores than well children. Lewis et al,[21] in a study of middle income children with asthma, found that parents were more likely to attribute certain types of impairment to illness than they were other types of impairment. Functional status scores and Impact-on-Family scores in our study were similar to those reported by Stein and Jessop and we observed that parents discriminate between different aspects of impairment, as described by Lewis et al. Because the effects of asthma are so pervasive, physicians should inquire about several aspects of day-to-day functioning, rather than focus solely on emergency department visits and hospitalizations. In children who were able to perform spirometry, pulmonary function variables did not predict any of the morbidity outcome variables, suggesting that other factors—behavioral and environmental—contribute to the impact of a chronic illness on children and their families.

Certain health behaviors, barriers to health care, and medical care factors may have contributed to the morbidity experienced by these children. Although parents reported high rates of compliance and perceived medication efficacy, reported avoidance of known asthma triggers was lower. Children and their parents differed significantly in some of their

opinions and self-reported behaviors. These differences may result from real differences in the experiences, behaviors, and attitudes of parents and children; a limitation in the ability of children to understand certain questions; or other unknown factors. These differences bear further exploration.

Many children (44%) were exposed to cigarette smoke in their homes. Smoking rates were similar to rates found among Mexican-American subjects in the Hispanic Health and Nutrition Examination Survey.[30] Because passive smoking has been shown to increase frequency of asthma symptoms and emergency department visits, these rates are worrisome.[31]

Most children with asthma experienced several barriers to optimal health care. Lack of insurance coverage, other financial barriers, and lack of a routine source of health care were common. According to data from the National Medical Expenditure Survey, Hispanic persons were more likely to be uninsured (25%) than non-Hispanic white or black persons (9% and 16%, respectively).[10] In view of the finding that 71% of our study participants did not have health insurance and that the majority were impoverished, it is not surprising that most families had concerns about paying for medications. Thirteen percent of children did not have a regular source of health care. Similarly, in the National Medical Expenditure Survey, Hispanic patients were less likely to have a usual source of health care than non-Hispanic white patients.[32] Lack of a consistent source of health care may pose a particular problem for children with a chronic disease, such as asthma.

Physician prescribing patterns also may have contributed to morbidity. Despite the severity of illness in these children, only half had been prescribed anti-inflammatory agents. Inflammation is now believed to be an important contributor to airway obstruction. The recommendations of the Expert Panel Report of the National Asthma Education Program[26] emphasize the use of anti-inflammatory agents for children with moderate or severe asthma. However, decisions to prescribe these medications must be tempered with an understanding of the high cost of inhaled cromolyn and steroids compared with topical β-agonists and oral theophylline. Indeed, paying for medications was the most common barrier reported by families in this study.

RECOMMENDATIONS

This study reveals several potential targets for intervention. Two factors, knowledge about asthma and exposure to cigarette smoke in the home, were significantly associated with outcome in these children and therefore should be addressed in interventions. Because increased knowledge about asthma was associated with a decrease in the impact of the illness on the family, and because knowledge is a necessary prerequisite for behavior change, intervention programs must address patient and family needs for information.

Passive exposure to cigarette smoke was a common finding and was significantly associated with impact of the illness on the family. Inasmuch as the success of smoking cessation interventions has been found to be related to both the number of sessions and the duration of contact with the program, the ongoing relationship of a physician with the parents of a child with asthma may be a good forum for smoking cessation advice.[33] Although the effect of a single patient-physician encounter on smoking behavior is probably small, some authors have shown that asking a patient if he or she smokes resulted in a significant increase (4%) in sustained abstinence.[34] At a minimum, physicians should encourage children with asthma and their families to limit the child's passive exposure to cigarette smoke.

This study also reveals several problem areas in the care of children with asthma. In our study, these factors were not significantly associated with outcome. However, based on our findings and those of other authors, these recommendations seem reasonable for all children with asthma. Physicians, through educational and behavioral interventions, should be encouraged to increase use of anti-inflammatory agents. Efforts should be made to reduce financial and other barriers to health care and to shift chronic care from emergency departments to individual medical providers.

Asthma self-management skills are another potential target for intervention. Although no single behavior or group of behaviors was significantly associated with morbidity, this study revealed several potential problem areas. These families had problems with early symptom detection and with avoidance of triggers. In other studies, improved self-management skills have been associated with decreased morbidity from asthma.[35]

This study clearly describes the morbidity experienced by a group of Hispanic children with asthma, the possible contributing factors, and the potential targets for intervention. Future studies should focus on the development and evaluation of interventions that are tailored to the needs of this rapidly growing and at-risk group of children.

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BARTHOLOMAEUS METLINGER ON TEETHING (1476)

Metlinger's *Ein Regiment der Jungen Kinder*, published in Augsburg in 1473, was the first German work on children to be printed in the vernacular. He described teething as follows[1]:

In many children the teeth come easily and with little distress but these fall out again. But when the teeth come up with difficulty and with great pains they are the more strong. Teeth come more easily in the spring, next in summer, and with the most difficulty in winter. When the teeth are trying to come, various disturbances occur in children such as swelling in the jaws and neck, and they stir up other ailments. If the jaws begin to swell, one should rub them with honey and salt, that takes away their pain and strengthens the jaw. And when the teeth have come through one should let the child chew the stem of violet or liquorice. And when the points of the teeth are coming through they are eager to chew and bite hard and one must be careful that they do not chew anything too hard, and one should rub their jaws with hare's brain or with hen's grease or with dog's milk: these have the property of making the coming of teeth easier and one may let them chew on soft violet root or liquorice stem.

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Noted by T. E. C., Jr., MD

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Murray, A.B., and Morrison, B.J., "The Decrease in Severity of Asthma in Children of Parents who Smoke Since the Parents Have Been Exposing Them to Less Cigarette Smoke," Clin Immunol 91: 102-110, 1993.

The authors studied every child with asthma between the ages of 1 and 17 years who had been referred to the allergy clinic at the Children's Hospital in Vancouver, British Columbia, between November 1, 1983, and June 30, 1990. Interviews were conducted with the accompanying adult. Skin prick tests were performed on the children, along with forced expiratory spirograms (in children 6 years of age or older). A bronchial challenge test was performed on children 7 years of age or older. The authors reported that although the actual number of cigarettes had not appeared to change, the number of cigarettes smoked in the same room as the child had decreased markedly. The authors report that "concurrent with the diminished exposure to smoke a decrease in the severity of asthma in children of smokers is shown by a significant decrease in the asthma score and a marked increase in the FEV1% and FEF25% to 75%." The authors conclude that "it appears that if parents are aware that smoke will aggravate their child's asthma, the child will be exposed to fewer cigarettes, and the asthma will be less severe."

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The decrease in severity of asthma in children of parents who smoke since the parents have been exposing them to less cigarette smoke

Andrew B. Murray, MB, FRCP(C), and Brenda J. Morrison, PhD
Vancouver, British Columbia, Canada

Background: *In 1985 we became aware that the smoking of parents aggravates their children's asthma. Since then we have advised all referring doctors to urge parents not to expose their asthmatic children to smoke.*
Methods: *We investigated 807 nonsmoking asthmatic children, from 1 through 17 years of age, who were consecutively referred between 1983 and 1990. We compared the children who were seen before July 1986 with those seen after that date.*
Results: *Those seen in the later period had intimate exposure to a far smaller number of cigarettes smoked per day, both by mothers (7 vs 3, $p = 0.005$) and by fathers (5 vs 2; $p = 0.001$). A concurrent improvement was observed in adjusted measures of asthma severity in their children (asthma score 7.5 vs 6.5, $p = 0.047$; forced expiratory volume in 1 second as a percent of predicted [FEV_1%] 79.2 vs 93.7, $p = 0.000$; and forced expiratory flow rate during middle half of forced vital capacity [FEF_{25-75}] 67.3 vs 82.0, $p = 0.009$), and for every cigarette less smoked in the room with the child the FEV_1 increased by 3%. When parents of those seen in the later period were asked whether they had been told that smoke would aggravate their child's asthma, 80% affirmed that they had. The difference in asthma severity between the two time periods was much less in children of nonsmokers than in children of smokers.*
[redacted]
(J ALLERGY CLIN IMMUNOL 1993; 91:102-10.)

Key words: *Smoke pollution, asthma severity, children, counseling*

Surveys of asthmatic children performed before 1986 report more severe symptoms and lower lung function test results if the children are exposed to smoke in the home.[1-4] Both the medical profession and the general public have become aware that smoke aggravates asthma. This is particularly apparent in the province of British Columbia where articles on the subject have been published in the medical and in the lay press,[5, 6] and where all doctors who refer patients to the allergy clinic at Children's Hospital in Vancouver have, since 1985, been urged to counsel parents of asthmatic children never to smoke when in the home.

Abbreviations used	
FVC:	Forced vital capacity
FEV_1:	Forced expiratory volume at 1 second
FEV_1%:	Ratio of forced expiratory volume in 1 second to forced vital capacity
FEF_{25-75}:	Forced expiratory flow rate during the middle half of the forced vital capacity
PC_{20}:	Provocation concentration of aerosolized histamine necessary to cause a 20% fall in FEV_1

Since 1983 we have been gathering data on passive smoking and on asthma severity in children who have attended our clinic. From 1983 until 1986 we observed more severe asthma in children of smokers than in those of nonsmokers, but since 1986 there has been a marked lessening in the severity of asthma in children of smokers, their asthma being no more severe than that in children of nonsmokers. It appears likely that much of this improvement is the result of the parents' awareness of the harmful effects of smoke.

From the Department of Pediatrics and the Department of Health Care and Epidemiology, University of British Columbia, Vancouver.
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Reprint requests: Andrew B. Murray, MD, British Columbia's Children's Hospital, 4480 Oak St., Vancouver, British Columbia, Canada, V6H 3V4.
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and a consequent decrease in exposure of asthmatic children to smoke.

MATERIAL AND METHODS

The series included every child with asthma, 1 to 17 years of age, who had been referred to the allergy clinic at the Children's Hospital in Vancouver, British Columbia, between Nov. 1, 1983, and June 30, 1990 and had been seen by A.B.M., one of two pediatric allergists who conduct alternate sessions at the clinic. All patients, new and old, were included in the series. The history, physical findings, and special investigation results used in the study were those recorded at a single visit. The parents were contacted 2 weeks before the appointment and then again 48 hours before the appointment and were instructed as to which medications to withhold so that these would not decrease bronchial responsiveness to histamine and skin test reactions.

Questionnaire

A trained interviewer asked standardized questions of the accompanying adult. In 99% of cases this was a parent, and in 92% of cases it was the mother, either alone or accompanied by the father. Parents were asked how many days during the past year the child had wheezed and had taken medication, whether corticosteroids had been given, whether the child wheezed on exertion, and how severe they thought the child's asthma had been. Each of their answers was given a number according to severity, and the sum of these numbers was the asthma score[7] (Appendix). In addition, they were asked about other features that might influence the severity of asthma, variables such as age of onset of asthma, number of respiratory infections, and the presence of animals in the house.

The last questions to the accompanying parents were about smoking. They were asked how many cigarettes each of them smoked per day, the total number and the number smoked when in the house.[7] From June 1985 to June 1986 they were also asked how many cigarettes they smoked when in the same room as the child. This question was discontinued at the end of June 1986 because parents hesitated considerably longer in answering this question than any other question, and because the correlation of asthma severity with this number of cigarettes was not significantly greater than with the number smoked when in the home. By 1988, however, it became obvious that parents were smoking fewer cigarettes when in the same room with their child than parents had done previously. Therefore this question was reintroduced to our standard questionnaire in January 1989.

Finally, the child was asked privately whether or not he or she smoked. The seven children who admitted to being smokers were excluded from the study. Also excluded were five who had cystic fibrosis and one who had marked gastroesophageal reflux.

Skin prick tests

By use of a standard method skin prick tests were performed with a negative (saline) and positive (histamine) control solution,[7] extracts of 1% *Dermatophagoides farinae* and *D. pteronyssinus* (Bencard Division of Beecham Laboratories, United Kingdom), and dog and cat hair (Hollister Stier, Spokane, Wash.). These and the other tests were performed by a technician who had no knowledge of the smoking habits of the family.

Forced expiratory spirogram

Children who were 6 years of age and older performed forced expiratory maneuvers until there were three recordings in which the forced vital capacity (FVC) agreed within 5%. This was achieved in five or fewer efforts by all except eight children. In these children who produced an acceptable spirogram, the tracing that had the greatest sum of FVC and forced expiratory volume at one second (FEV_1) was used for all measurements.[8] The FVC, FEV_1, and the forced expiratory flow rate during the middle half of the FVC ($FEF_{25\%-75\%}$) were expressed as a percentage of the predicted mean for age, sex, and height.[10]

The spirogram was recorded with Pulmanor, Datamite III and Datamite V spirometers (Jones Medical Instrument Co., Oak Brook, Ill.), all of which were calibrated weekly with a known volume of carbon dioxide discharged at a standard velocity from a Jones Calibrator. The results were analyzed and printed by Datamatic computers (Jones Medical Instrument Co.) that were connected to the spirometers.

Bronchial responsiveness to histamine

A bronchial challenge test was performed on the children who were 7 years of age and older, except for those who had taken bronchodilators or antihistamines so recently that there was a risk of the test results being affected, those who reported a cold or respiratory infection within the preceding 2 weeks, and those whose FEV_1 was less than 1 L in volume or was less than 60% of predicted value. One hundred seventy-eight subjects were tested. We used a modification of the protocol of Cockcroft et al.[11] to give the patient's responsiveness to histamine acid phosphate aerosol generated by air flowing at 8 L/min through a Wright nebulizer (Aerosol Products Ltd., London, England). Doubling concentrations were administered by a loosely fitting mask until we reached the provocation concentration required to cause a 20% decrease in FEV_1 (PC_{20}). The strongest concentration administered was 8 mg/mL. Children whose FEV_1 did not decrease by 20% when this concentration was administered were eliminated from analyses of bronchial responsiveness. There were few such children. Two of the children had mothers who smoked, and 14 had mothers who did not smoke. Informed consent was obtained from the parents or guardians of the children who served as subjects for this investigation.

Expired air carbon monoxide concentration

To verify that subjects who claimed to be nonsmokers were being truthful, the carbon monoxide (CO) levels in expired air were measured on all children who were 9 years of age and older and were seen in 1988, 1989, and 1990. After 10 seconds of breathholding, the subject blew into a Vitalor CO monitor (Vitalograph Medical Instrumentation, Buckingham, England).[12] The monitor was calibrated weekly. None of those who claimed to be nonsmokers had a CO level higher than 8 ppm, whereas all who admitted to being smokers did.

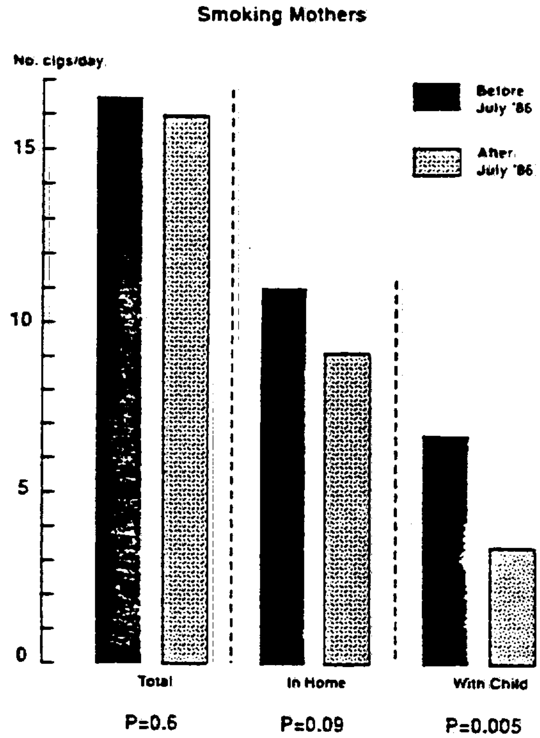

FIG. 1. Number of cigarettes smoked per day by mothers who smoked. Number smoked in total and when in the house was known for 204 of the 205 mothers, and number smoked when in the same room as the child known for all 93 children seen from June 1, 1985, through June 30, 1986, and from Jan. 1, 1989, through June 30, 1990.

Statistical analysis

After exclusion of the children who were themselves smokers, those with cystic fibrosis, and the one who had marked gastroesophageal reflux, 807 remained. Four hundred fifteen of these were seen before July 1986, and 392 were seen after July 1986. Henceforth these will be referred to as the earlier and the later groups.

In a preliminary analysis, Student *t* tests were used to test the difference between means, and Pearson product-moment correlation coefficients were calculated to measure the association between the measures of asthma severity and the logarithms of the number of cigarettes the mother or father smoked. For the main analysis, analysis of covariance (ANCOVA) was used. The model incorporated two factors, sex and time period (before or after July 1986) and two covariates, age and age of onset of asthma. Then, to account for smoking exposure, the logarithm of the number of cigarettes the mother smoked when in the same room as the child, and the logarithm of the number of cigarettes the father smoked when in the same room as the child, were included as covariates in one of the analyses of those children who had a parent who smoked. The number available for the main analysis was 570 because information on the number of cigarettes smoked when in the same room as the child had been sought only during the periods June 1985 through June 1986 and January 1989 through June 1990.

RESULTS

Two sets of analyses were performed. The first was a preliminary one to determine whether parents were smoking fewer cigarettes and whether there had been a concomitant lessening in the severity of the children's asthma. After this a second analysis was carried out to assess if the change in asthma severity could be explained by the change in the parents' smoking habits. This was done by integrating the smoking and asthma severity data in analyses of covariance.

Preliminary analysis

The preliminary set of analyses showed that although there was little change in the total number of cigarettes the parents smoked per day when comparing the earlier and later periods, 17 versus 16 by mothers ($p = 0.6$) and 20 versus 19 by fathers ($p = 0.3$), the mean number of cigarettes smoked when in the same room as the child decreased markedly, 7 versus 3 by mothers ($p = 0.005$) and 5 versus 2 by fathers ($p = 0.001$, Fig. 1, Table I). Concurrent with the lessened exposure to the mothers' smoke there was a marked improvement in the children's lung function (Fig. 2, Table II A). A similar but lesser improvement was observed in children whose fathers smoked (Table II B). Not only was there evidence of much better air flow in those seen in the later than in the earlier period, but a dose-response gradient was also present: the correlations representing this gradient are given in Table III. As well, significant correlations occurred between the number of cigarettes the mother smoked in the house and the child's asthma score ($p = 0.021$), $FEV_1\%$ ($p = 0.011$), and FEF_{25-75} ($p = 0.046$), although not the logarithm of the PC_{20} ($p = 0.43$).

To determine whether a difference in some other parameter might be contributing to the apparent improvement that occurred in smokers' children, the means of other possibly relevant variables were compared for children seen in the two time periods. They were the following: age, sex, presence of allergic nasal symptoms, a history of atopic dermatitis, a family history of asthma, number of siblings, recent respiratory infection, number of colds per year, ownership of a dog by children with a positive skin test to dog, ownership of a cat by children with a positive skin test to cat, positive skin test to house dust mite, age of onset of asthma, wood stove used for heating the house, and a gas range used for cooking. The means

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TABLE I. Number of cigarettes smoked by parents of children seen before and after July 1986

Measurement	No. of cigarettes per day Mean and SE Before July 1986 (no. subjects)	After July 1986 (no. subjects)	2-tail probability
Mother			
Total no.	16.6 ± 1.0 (92)	15.9 0.8 (113)	0.568
At home	11.0 ± 0.8 (80)	9.0 0.7 (113)	0.060
Same room with child	6.6 0.9 (40)	3.4 0.6 (53)	0.005
Father			
Total no.	20.2 ± 1.1 (118)	18.8 ± 0.9 (135)	0.329
At home	8.3 ± 0.6 (99)	6.1 ± 0.5 (133)	0.004
Same room with child	4.6 ± 0.6 (47)	2.0 ± 0.4 (64)	0.001

Numbers given are total number smoked per day, number smoked when in the house, and number smoked when in the same room as the child.

TABLE II A. Unadjusted means of indicators of asthma severity in 807 children seen before and after July 1986

Measurement	Before July 1986 Mean	SE	No. subjects	After July 1986 Mean	SE	No. subjects	2-tail probability
Mother smoker							
Asthma score	8.2	0.3	92	5.8	0.2	112	0.000
FEV$_1$%	77.3	2.1	69	91.3	1.5	59	0.000
FEF$_{25-75}$	59.5	3.1	69	81.0	3.1	59	0.000
Log PC$_{20}$	− 0.23	0.27	26	0.41	0.27	24	0.098
Mother nonsmoker							
Asthma score	6.4	0.2	321	6.6	0.2	275	0.51
FEV$_1$%	84.4	1.1	224	90.8	1.2	148	0.000
FEF$_{25-75}$	71.7	1.8	224	79.4	2.0	148	0.005
Log PC$_{20}$	0.44	0.14	66	0.26	0.21	46	0.450

Data for asthma score or mother's smoking status unavailable on seven subjects.

TABLE II B. Unadjusted means of indicators of asthma severity in 807 children seen before and after July 1986

Measurement	Before July 1986 Mean	SE	No. subjects	After July 1986 Mean	SE	No. subjects	2-tail probability
Father smoker							
Asthma score	7.1	0.3	118	6.5	0.2	134	0.065
FEV$_1$%	80.2	2.0	84	93.0	1.7	64	0.000
FEF$_{25-75}$	67.1	3.0	84	84.1	2.8	64	0.000
Log PC$_{20}$	0.12	0.18	32	0.74	0.26	23	0.050
Father nonsmoker							
Asthma score	6.7	0.2	283	6.3	0.2	253	0.183
FEV$_1$%	84.2	1.0	201	90.1	1.2	143	0.000
FEF$_{25-75}$	70.0	1.8	201	78.0	2.1	143	0.004
Log PC$_{20}$	0.32	0.17	60	0.10	0.20	47	0.403

Data for asthma score or father's smoking status unavailable on 19 subjects.

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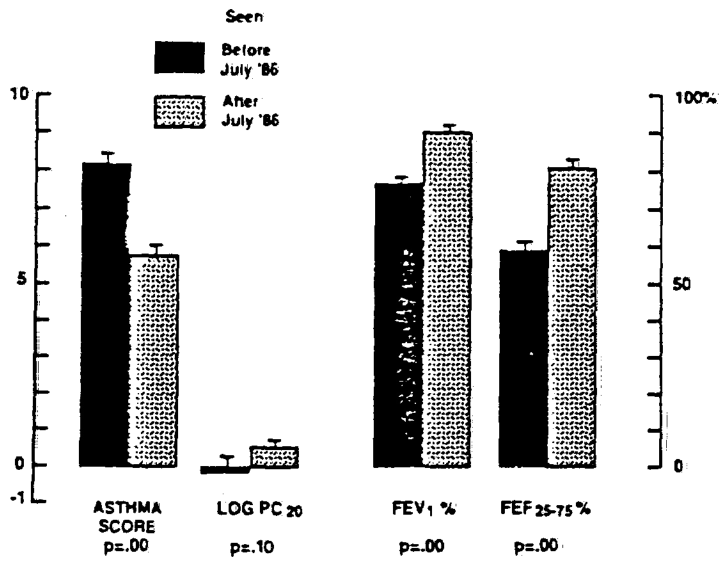

FIG. 2. Indicators of asthma severity in children of mothers who smoked.

were similar for all these variables except for age: those seen during the later period were, on average, 2 years younger than those seen during the earlier period ($p < 0.01$). The probable reason for this difference is that some of those seen in the earlier period were children whose first visit to the clinic had been before the start of the study, whereas those seen in the later period were all new patients.

Main analysis

Three analyses of covariance were carried out for each of the four measures of asthma severity. One was on children of nonsmokers, and the other two were on children of smokers. The overall purpose of the analyses was to determine changes in asthma score and in lung function test results after adjustment for variables found previously to affect asthma severity. These variables were sex, age, and age of onset of asthma.[13, 14] The model incorporated sex and time period as the factors and age and age of onset as covariates in the three analyses. In the second analysis on smokers' children we included the logarithm of the number of cigarettes the mother smoked when with the child and the logarithm of the number of cigarettes the father smoked when with the child. The results of the 12 analyses are given in Table IV. The first two columns indicate that smokers' children (column 2), compared with nonsmokers' children (column 1), had greater improvement in asthma score and in spirometric test results across the time period. The third column indicates that this difference across the time periods in smokers' children is decreased if the number of cigarettes smoked when with the child is taken into account, as would be expected if exposure to the parents' cigarette smoke is a reason for the difference.

No significant improvement in PC_{20} was seen across the time periods in either nonsmokers' or in smokers' children, but in the smokers' children the mean values of the log PC_{20} were higher in the later period.

DISCUSSION

Since we became aware, in 1985, that asthma is aggravated by secondhand smoke we have been advising all our referring doctors to urge parents who are smokers who have asthmatic children not to expose their children to their smoke.[5] Although the parents we have seen after July 1986 have continued to smoke the same total number of cigarettes as those seen before July 1986, they seem to have responded to their doctor's advice and to increased general awareness of the ill effects of secondhand smoke: they have smoked fewer cigarettes when in the house, and considerably fewer cigarettes when in the same room as their child.

Concurrent with the diminished exposure to smoke a decrease in the severity of asthma in children of smokers is shown by a significant decrease in the asthma score and a marked increase in the $FEV_1\%$, and $FEF_{25\%-75\%}$. By entering into the model the number of cigarettes the mother and father smoked each day in the child's presence, the differences between spirometric values recorded before and after July 1986 were decreased, indicating that diminished exposure to cigarette smoke was an important factor in the improvement observed in the spirometric test values. As

TABLE III. Correlations between numbers of cigarettes smoked per day while in the same room as the child and indicators of asthma severity

Measurement	Mother			Father		
	r	*n*	*p*	*r*	*n*	*p*
Asthma score	0.19	93	0.037	−0.040	111	0.337
FEV_1%	−0.32	59	0.008	−0.344	67	0.002
FEF_{25-75}	−0.30	59	0.010	−0.234	67	0.028
Log PC_{20}	0.11	23	0.308	−0.061	17	0.408

Number of cigarettes smoked when in the same room as the child recorded only for patients seen from June 1, 1985, through June 30, 1986, and from Jan. 1, 1989, through June 30, 1990.

a result of including in the model the regression on the number of cigarettes, the FEV_1 improved by 3%, on average, for each decrease of one cigarette the mother or father smoked when in the room with the child.

Eighty percent of the parents who were questioned about their smoking after 1988 said that they had been told by their doctor not to expose their child to smoke, and that they attempted to avoid doing so by smoking outdoors or in another room or by using maneuvers such as smoking by an open window or blowing their smoke into the fire or into the exhaust fan in the kitchen. Unfortunately, we had not previously asked this question; it was suggested to us after 1986 by increasing numbers of parents who volunteered this information on being asked how many cigarettes they smoked in the same room with the child. In children seen after 1986, therefore, it is probable that in many cases the true exposure to cigarette smoke was even less than was indicated by the number of cigarettes smoked when in the same room as the child. If parents who were questioned after 1986 had not used avoidance measures it is likely that the correlation between the number of cigarettes smoked and asthma severity would have been even stronger, and that incorporating the number of cigarettes into the model (Table IV: column 3) would have reduced even further the differences between spirometric measurements recorded before and after July 1986.

Not only was asthma less severe in smokers' children who were seen after July 1986, but also their lung function measurements were no longer lower than those found in nonsmokers' children. This large degree of improvement may be explained by smoke having caused the asthma, as well as aggravating asthma, in some smokers' children. Where smoke is the cause of asthma the wheezing should be expected to cease, or greatly improve, when exposure to smoke stops or lessens. Smoke certainly seems to be a cause of asthma in children who have had atopic dermatitis.[15] As well, Barbee et al.[16] found that the prevalence of wheezing decreased in adults who stopped smoking; the decrease was particularly marked in those who had negative skin tests to common local airborne allergens. This disproportionately large decrease of wheezing in subjects with negative skin tests suggests that they had stopped wheezing because the cause of their asthma, cigarette smoke, had ceased, but some who had positive skin tests still wheezed because of continued exposure to their specific allergen. The allergen that most commonly causes asthma in our area, and in other places is house dust mite,[17, 18] and a positive skin prick test reaction to mite was considerably more common in our asthmatic children whose mothers were nonsmokers than in those whose mothers were smokers: the proportions were 42% and 28%, respectively ($p = 0.01$). It is therefore likely that when smoke exposure decreased, those whose asthma was caused by smoke improved more than those whose asthma was caused by mites. Because mite allergy was more common in nonsmokers than in smokers' children, it is understandable that asthma severity could become comparable in the two groups, or could become even less severe in smokers' children.

Cigarette smoke from the parents appears to aggravate the children's asthma more than does cigarette smoke from other sources (Murray AB, Morrison BJ. Unpublished data), but it is nonetheless possible that secondhand smoke from other people also has an effect. The latter type of exposure is difficult to quantitate: parents seldom know how many cigarettes their children are exposed to at day-care centers, at babysitter's homes, and in public places. It is probable, however, that such exposure has progressively decreased as public awareness about the ill effects of smoke pollution has become more general, as smoking in public places has been banned, and as the prevalence of smoking in Canada has decreased. Between 1986 and 1989 the average number of cigarettes smoked per person per day has decreased from nine

TABLE IV. Indicators of asthma severity; mean values adjusted for sex, age, and age of onset of asthma

	Column 1: neither parent smokes July 1986 before vs after	Column 2: either parent smokes July 1986 before vs after	Column 3: either parent smokes Adjusted for cigarettes* July 1986 before vs after
Asthma score	6.45 vs 6.62 (n = 418, p = 0.55)	7.48 vs 6.49 (n = 146, p = 0.047)	7.50 vs 6.48 (n = 146, p = 0.064)
FEV_1%	84.7 vs 89.9 (n = 260, p = 0.005)	79.2 vs 93.7 (n = 93, p = 0.000)	80.8 vs 92.2 (n = 93, p = 0.003)
$FEF_{25\%-75\%}$	71.2 vs 77.6 (n = 260, p = 0.041)	67.3 vs 82.0 (n = 93, p = 0.009)	68.7 vs 80.65 (n = 93, p = 0.052)
Log PC_{20}	0.41 vs 0.16 (n = 71, p = 0.45)	0.18 vs 0.32 (n = 30, p = 0.78)	0.21 vs 0.30 (n = 30, p = 0.84)

*Adjusted for the number of cigarettes parents smoked when in the same room with child. Number recorded on patients seen from June 1, 1985, through June 30, 1986, and from Jan. 1, 1989, through June 30, 1990.

to seven.[18] This decrease may have accounted for some of the improvement observed in nonsmokers' children as well as in smokers' children. Not surprisingly, however, the improvement was much greater in those whose parents were smokers.

When comparing mean PC_{20} values before and after July 1986 in our population of smokers' children as a whole, significant improvement occurred in the later period for children of fathers who smoked but not those of mothers who smoked. Also, no significant correlation occurred between the number of cigarettes the mother or father smoked and the child's PC_{20}. A reanalysis of the data, including children whose bronchi did not respond significantly to 8 mg/ml histamine, produced similar results. This lack of correlation is unexpected because a significant correlation between the number of cigarettes smoked by the mother and bronchial responsiveness in the child has been reported in studies performed before 1986 by us,[1, 13] and a significant difference between the bronchial responsiveness in children of mothers who smoked and those who did not has been observed by O'Connor et al.[3] and by Martinez et al.[4] A possible explanation for the lack of association in our present population is that lifelong exposure to a chemical in the parents' cigarette smoke had induced long-lasting hyperresponsiveness in some of the children's bronchi, a hyperresponsiveness that was not reversed by a comparatively recent decrease in exposure to smoke pollution. Adults with chemically induced hyperresponsiveness, and whose exposure to the chemical has ceased, often have a normal FEV_1 but a persistently abnormal PC_{20}.[20]

Because factors other than smoke may possibly have influenced our results, they should also be considered. One is that air pollution may have decreased over the study period. However, no change occurred in O_3, SO_2, and NO_2 levels monitored daily throughout the study period at 11 sites in the Greater Vancouver Regional District[21] (Bates DV, 1992. Unpublished data). Another is that exposure to airborne allergens may have decreased with time. Although this possibility cannot be ruled out, we detected no obvious difference between the two time periods in the amounts of pollens that we trapped by the gravity method, and in smokers' children the frequency and size of positive skin test reactions to mite were slightly greater in the later than in the earlier period. A third factor to be considered is the increased frequency with which corticosteroids have been given to asthmatic patients in recent years. Use of corticosteroids by children of nonsmokers increased, 8% of them used them in the earlier period and 15% took corticosteroids in the later period, and it is likely that this more frequent use of corticosteroids contributed to the improved spirometric measurements that were observed in children of nonsmokers who were seen after July 1986. In children of smokers, by contrast, a marked decrease of frequency occurred with which corticosteroids were used by those seen in the later than in the earlier period (20% vs 5%, p = .00). This significant decrease is further evidence that severity of asthma lessened in smokers' children when they were exposed to fewer cigarettes. Fourth, the pattern of use of another class of medication may also have changed, that of the beta-agonist bronchodilators. We have no data on these bronchodilators specifically, but this was the class of medication most commonly used by the patients that

had been referred to us, and medication use is reflected in the asthma score (Appendix). When comparing the later with the earlier time period, the asthma score decreased significantly in children of smokers, but increased slightly in the children of nonsmokers, the children who made up the large majority of our subjects. Fifth, it is possible that parents underestimated the number of cigarettes to which they exposed their children each day, particularly during the later period. We do not think that untruthful reporting caused a serious bias because 7-year-old children are nowadays usually well aware of the harmful effects of smoking and are quick to correct their parents' estimate if the reported number of cigarettes is falsely low. As well, a highly significant correlation occurred between the number of cigarettes reported and the spirometric test results. Sixth, we have no objective data on the frequency of viral respiratory infections, but we did inquire about the frequency of colds. These were reported to be slightly more frequent in the later than in the earlier period in smokers' children.

There is evidence that since 1986 an increasing awareness of the harmful effects of secondhand smoke has caused parents to smoke fewer cigarettes when with their asthmatic children, and that the resulting decrease in exposure has been associated with a marked improvement in the severity of asthma of the smokers' children who have been referred to our clinic.

We thank Janice Fuller, RN, for asking the standardized questions, Mrs. Huguette Brown and Mrs. Radana Vaughan for performing the tests, and Mr. Ronnie Sizto for computer programming.

APPENDIX: Asthma score*

History	Score 0	1	2	3	4
Parent's assessment of severity	None	Mild	Moderate	Severe	
Wheezing, number of days	None	1-3	4-182	183-365	
Medication, number of days	None	1-3	4-30	31-182	183-365
Corticosteroid medication	None			Yes	
Wheezing on exertion	None	Yes			

*Numeric score indicating severity assigned to each feature in the history.

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Defective antipneumococcal polysaccharide antibody response in children with recurrent respiratory tract infections

Lieke A. M. Sanders, MD, Ger T. Rijkers, PhD, Wietse Kuis, MD, PhD, Annemarie J. Tenbergen-Meekes, MSc, Babette R. de Graeff-Meeder, MD, PhD, Idske Hiemstra, MD, and Ben J. M. Zegers, PhD *Utrecht, The Netherlands*

Background: *Recurrent pyogenic infections are known to occur in patients with an impaired response to polysaccharide antigens. We investigated the occurrence of deficient responses to pneumococcal capsular polysaccharides in patients with recurrent respiratory tract and recurrent systemic infections.*

Methods: *Forty-five patients, 1.7 to 17.1 years of age, were immunized with 23-valent pneumococcal polysaccharide vaccine. Antibody levels to seven pneumococcal serotypes (3, 4, 6A, 9N, 14, 19F, 23F) were determined by ELISA before and after immunization. In addition, patients received a booster immunization with diphtheria toxoid, tetanus toxoid, and poliomyelitis virus vaccine.*

Results: *Thirty-five patients had normal serum immunoglobulin levels. Five of these patients (14%) had low antipneumococcal preimmunization antibody levels and failed to respond to pneumococcal vaccination, whereas the response to booster immunization with protein antigens was appropriate. Three patients were younger than 3 years old, and one had a family history of IgG2 deficiency. Low IgG developed in a fifth patient during follow-up. Ten patients had a humoral immunodeficiency. Seven of these patients failed to respond to pneumococcal vaccination.*

Conclusions: *We conclude that a defective immune response to polysaccharide antigens in patients requires long-term follow-up to distinguish transient maturational delay from a persistent selective impaired response to polysaccharide antigens, which on occasion may precede the development of humoral immunodeficiency disease. (J ALLERGY CLIN IMMUNOL 1993;91:110-9.)*

Key words: Pneumococci, antepolysaccharide antibodies, respiratory tract, Fallot, immunodeficiency, cell wall polysaccharide, otitis

The development of antibodies to polysaccharides of encapsulated bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae* type b in early life is much poorer than to proteins. For many polysaccharide antigens, adequate antibody titers are not attained until the age of 18 to 24 months or later after infection or vaccination with polysaccharide vaccines.[1-6] The key component of the host defense against encapsulated bacteria is opsonophagocytosis of the microorganism for which the presence of specific anticapsular antibodies, complement and phago-

From the Department of Immunology, University Hospital for Children and Youth, "Het Wilhelmina Kinderziekenhuis," Utrecht, The Netherlands.

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Reprint requests: E. A. M. Sanders, University Hospital for Children and Youth, "Het Wilhelmina Kinderziekenhuis," Department of Immunology, P. O. Box 18009, 3501 CA Utrecht, The Netherlands.

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Infante-Rivard, C., "Childhood Asthma and Indoor Environmental Risk Factors," American Journal of Epidemiology 137(8): 834-844, 1993.

In this case-control study, the authors studied the possible relationship between various environmental factors and the incidence of asthma among 3- and 4-year-old children. Cases were 457 children who had been diagnosed for the first time with asthma upon an emergency room visit. Controls were chosen from family allowance files and were matched with children on age and census tract. The childrens' parents were interviewed by telephone, and a subsample of children was selected to wear a nitrogen dioxide monitoring badge for a 24 hour period. The authors reported that "after personal susceptibility factors were controlled for, the following were independent risk factors for asthma: the mother's heavy smoking (odds ratio (OR) = 2.77, 95% confidence interval (CI) 1.35-5.66). . ." However, the authors also reported that the presence of other smokers in the household was "not quite significant (OR = 1.82, 95% CI 0.98-3.38)."

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Childhood Asthma and Indoor Environmental Risk Factors

Claire Infante-Rivard

In a case-control study carried out in Montréal, Québec, Canada, between 1988 and 1990, indoor environmental factors were studied in relation to the incidence of asthma among 3- and 4-year-old children. Cases (n = 457), whose parents were recruited at a hospital emergency room, were children who had a first-time diagnosis of asthma (*International Classification of Diseases*, Ninth Revision, code 493) made by a pediatrician. Controls (n = 457) were chosen from family allowance files and were matched with case children on age and census tract. A telephone interview was administered to the children's parents. A 20% feasibility subsample was chosen to wear a nitrogen dioxide monitoring badge during a 24-hour period. Multiple conditional logistic regression analysis showed that after personal susceptibility factors were controlled for, the following were independent risk factors for asthma: the mother's heavy smoking (odds ratio (OR) = 2.77, 95% confidence interval (CI) 1.35–5.66), use of a humidifier in the child's room (OR = 1.89, 95% CI 1.30–2.74), and the presence of an electric heating system in the home (OR = 2.27, 95% CI 1.42–3.65). The presence of other smokers in the home was not quite significant (OR = 1.82, 95% CI 0.98–3.38). A history of pneumonia, the absence of breast feeding, and a family history of asthma were also significant risk factors. In a separate unmatched multivariate analysis of subjects who had worn the nitrogen dioxide badge, there was a dose-response relation between nitrogen dioxide (in parts per billion) and asthma. These results confirm the role of susceptibility factors in asthma and show that indoor environmental factors contribute to the incidence of asthma. *Am J Epidemiol* 1993;137:834–44.

air pollutants; asthma; child; environment; household articles; nitrogen dioxide; tobacco smoke pollution

Concern has arisen in recent years about indoor air pollution as a risk factor for asthma (1). Pollutants in the home are numerous, and their sources, such as tobacco smoking, are encountered frequently. Moreover, the energy crisis of the 1970s provoked changes in the way houses are insulated and built; one consequence is that air exchange rates in energy-efficient "tight" and "super-tight" homes are substantially reduced in comparison with those in older conventional homes. Finally, it is recognized that most people spend 75–90 percent of their time indoors (2), a proportion that is likely to be greater in small children.

Indoor environmental factors that have received the most attention in the past are tobacco smoke and directly or indirectly measured nitrogen dioxide, mainly from gas appliances. The present study considered

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Abbreviations: CI, confidence interval; OR, odds ratio; ppb, parts per billion.

From the Department of Community Health, Hôpital Sainte-Justine, and the School of Occupational Health, McGill University, Montreal, Quebec, Canada.

Reprint requests to Dr. Claire Infante-Rivard, School of Occupational Health, McGill University, 1130 Pine Avenue West, Montreal, Quebec, Quebec, Canada H3A 1A3.

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these and other, less frequently studied potential risk factors for their relation to the incidence of asthma among 3- and 4-year-old children. The objective of the study was to estimate the contribution to asthma incidence of chemical, physical, and biologic indoor environmental factors, as well as family history of asthma and past infections, after accounting for personal susceptibility. A case-control study was carried out to meet this objective.

MATERIALS AND METHODS

Case ascertainment

Cases were 3- and 4-year-old children with a first-time diagnosis of asthma made by a pediatrician. We chose this age group to avoid the problem of differential diagnoses for asthma which is more likely at younger ages, and to allow for a plausible but reasonably short time period for risk factor assessment. Cases were recruited between January 1988 and December 1990 at the emergency room of Hôpital Sainte-Justine, the larger of two university-affiliated pediatric centers in Montreal, Quebec, Canada. A computerized roster is kept in the hospital's emergency room which includes the age of the child, the discharge diagnosis, and the child's medical record number. From this roster, 3- and 4-year-old children with a diagnosis compatible with any of those listed under *International Classification of Diseases*, Ninth Revision, code 493 had their hospital medical records checked for previous attendance with a similar diagnosis. Known (previously diagnosed) cases were rejected. A second screening for eligibility took place when the parents were asked whether the child had ever been diagnosed by a physician as having asthma. An additional criterion for eligibility was that the child reside in the greater Montreal region.

Control ascertainment

Controls were children of the same age (± month) and the same census tract (in the urban area) or postal code (in the rural area) as the case at the time of diagnosis. A census tract is defined in the *Canadian Census Dictionary* (3) as a small geostatistical unit including a mean of about 4,000 persons with maximum economic and social homogeneity. In rural areas surrounding the city, a postal code area indicates a region served by the post office or the postal branch. Controls were chosen from computerized family allowance files for the target region. The family allowance is a government stipend awarded to all families with children. Eligibility for the family allowance program is based on the following: a child must be less than 18 years of age and must reside in Canada. In addition, at least one parent must be a Canadian citizen, a person admitted to Canada as a permanent resident according to the terms of the law, or a person who has been admitted to the country as a visitor or who is holding a visiting permit for at least 1 year, and whose revenue is taxable (4). For reasons of cost, the latest available files from 1987 were used during 1988 and most of 1989. The 1989 files were used until the end of the study in 1990. All children who were eligible on the basis of age and census tract or postal code were enumerated from 1 to n. To choose the first control, we randomly generated a number between 1 and n. If, based on a search of readily accessible sources of information on addresses and telephone numbers, this control was not available, the procedure was repeated.

Data collection

The list of potentially eligible cases and controls was given to a first interviewer, who contacted the parents to confirm that the case was one with a first-time diagnosis by a physician and that the control had had no previous diagnosis of asthma made by a physician. If the parents were willing to participate, an appointment for the interview was made. A telephone interview was conducted by a second interviewer who was blind to the case/control status of the child. The interview had to take place for both cases and controls within 1 month of the case child's visit to the emergency room.

The questionnaire measured potential risk factors in yearly periods from birth to the time of diagnosis. These factors were grouped into three categories. The first category was personal susceptibility factors, family history of asthma, and past infectious diseases: the child's allergies, e.g., to food or clothing; parental and sibling asthma; and history of eczema, pneumonia, and tonsillectomy. The second category, environmental exposures in the home of a chemical nature, included maternal and paternal smoking; other smokers in the home; exposure to gas cooking appliances, kerosene space heaters, insulation material, and a fireplace or wood stove; and year of home construction. Other environmental factors of a physical nature were type of home heating system; whether the house contained a central humidifier, air purifier, or air conditioning; and whether a humidifier was used in the child's room. Other biologic factors assessed included family pets, wall-to-wall carpeting, the amount of dampness on the windows, and occupant density per room.

In addition, during the winter months, mostly the winter of the last study year, a subsample of 20 percent of study parents were asked to have their children wear a passive nitrogen dioxide monitoring badge (5) for 24 hours as part of a feasibility study. The main sources of emission of nitrogen dioxide in the home are gas stoves, gas- and kerosene-fueled space heaters, and, to a lesser extent, tobacco smoking (6). According to our instructions, the badge could either be worn by the child when he or she was awake and playing or left in the room while the child was sleeping. All consecutively interviewed parents during that study period were asked to use the badge, regardless of the child's case/control status.

Nitrogen dioxide from the filter badge was analyzed spectrophotometrically in parts per billion (ppb). The sensitivity of the badge was 66 ppb per hour, and in one study it was reported to have a precision of 5.9 percent (mean percentage difference, in ppb, between replicate measures; standard deviation, 5.4 percent) (7). The child's case/control status was unknown to the laboratory personnel who conducted the tests. The nitrogen dioxide results, in ppb, were categorized as follows: <0.5, 0.5–10, >10–15, and >15.

The third category included information on other personal and social factors such as the sex of the child, mother's and father's educational level (elementary school, high school or equivalent, college or equivalent, and postgraduate schooling), and breast feeding.

Some of the environmental exposures, such as type of heating and the presence of cooking appliances, wood stoves, fireplaces, central air conditioning, and central humidifiers, were also ascertained for any day-care center attended by the child, where applicable.

Statistical analysis

Conditional logistic regression (8) was used to analyze the matched data sets (EGRET package; Statistics and Epidemiology Research Corporation, Seattle, Washington). Odds ratios and their 95 percent confidence intervals were estimated. All statistical tests were two-sided. All variables were defined as categorical indicators. Categories were defined a priori. The independent contribution of each variable was assessed after controlling for personal susceptibility factors such as history of allergies and eczema. A multivarite model was developed that included all variables except those relating to insulation materials and the year of construction of the first home inhabited by the child, since parents often could not provide information on these factors. Nitrogen dioxide was not included either, because only 140 subjects had their child wear the badge as instructed. However, using the 140 subjects with nitrogen dioxide measurements, an unconditional logistic regression analysis was conducted that included nitrogen dioxide and all of the variables that made an independent contribution in the conditional multivariate model.

Response

There were 631 confirmed eligible case children; parents of 627 were successfully

interviewed, and four families refused to participate. However, 457 cases were used in the analysis because the controls for 170 of the cases could not be interviewed within 1 month of case ascertainment. This was mostly due to a delay in receiving and difficulty reading the computer tapes of the family allowance files at the beginning of the study and during the study's second year. Cases not included in the analysis were similar to those included with respect to age and sex distribution, the proportion with past allergies, and mother's smoking. On the other hand, we had to approach 1,188 families to obtain interviews from 457 controls: 598 families were no longer living at the address listed in the files, 53 had a confidential telephone number, 49 were known cases of asthma, 21 refused to participate, and 10 were not fluent in French or English.

Parents of 82 cases and 102 controls (20 percent of the study subjects) were asked if they would have their child wear the passive monitoring badge. Parents of two cases and five controls refused, and parents of 61 cases (61/80, 76.2 percent) and 79 controls (79/97, 81.4 percent) returned the badge.

RESULTS

All results for environmental factors (except for nitrogen dioxide, as explained above) are based on the presence or absence in the home of a given risk factor throughout the period between birth and the case's calendar date of diagnosis.

Child allergies (odds ratio (OR) = 1.88, 95 percent confidence interval (CI) 1.27–2.77) and eczema (OR = 2.06, 95 percent CI 1.37–3.10), each adjusted for the other, were independent risk factors for asthma. The percentages of parents and siblings with asthma and the prevalence of past infectious diseases for cases and controls are shown in table 1, along with matched odds ratios adjusted for child allergies and eczema. There were more cases than controls with a family history of asthma, as well as past pneumonia and tonsillectomy. All odds ratios were statistically significant.

Similar results for chemical, physical, and biologic factors in the home are shown in table 2. Slightly more case mothers than control mothers smoked, but the reverse was true for fathers. The adjusted odds ratio for a mother's smoking more than 20 cigarettes daily in comparison with not smoking was increased, at 1.60, and was almost significant ($p = 0.06$). There were twice as many other smokers in the homes of cases as in the homes of controls, and the odds ratio associated with this variable was significantly increased.

In analyses for which results are not shown, we derived a score based on the number of cigarettes smoked daily and the duration of the habit during the period between birth and time of diagnosis. Since smoking habits did not vary much, this analysis did not substantially change the results shown above.

The odds ratios for nitrogen dioxide increased with each categorized level in comparison with the baseline category. In the subgroup tested with the sampler, only six families had a gas stove. However, five of these six were in the highest category of

TABLE 1. Prevalence of a family history of asthma and past infectious diseases, matched odds ratios adjusted for allergy and eczema, and 95% confidence intervals among 457 cases diagnosed with asthma and 457 controls matched for age and area of residence, Montreal, Quebec, Canada, 1988–1990

Factor*	Cases (n = 457) (%)	Controls (n = 457) (%)	Matched odds ratio	95% confidence interval
Father with asthma	8.7	2.8	2.86	1.51–5.41
Mother with asthma	9.8	5.2	1.89	1.12–3.19
Siblings with asthma	9.6	5.4	1.91	1.15–3.19
Tonsillectomy	4.6	1.7	3.69	1.46–9.36
Pneumonia	24.0	8.3	3.31	2.17–5.06

* Factors are defined as yes versus no.

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TABLE 2. Prevalence of indoor chemical, physical, and biologic factors, matched odds ratios adjusted for allergy and eczema, and 95% confidence intervals among 457 cases diagnosed with asthma and 457 controls matched for age and area of residence, Montreal, Quebec, Canada, 1988–1990

Factor*	Cases (n = 457) (%)	Controls (n = 457) (%)	Matched odds ratio	95% confidence interval
Mother smoking (cigarettes/day)				
0	59.8	63.3	1.00	
>0 to ≤20	30.2	29.6	1.11	0.82–1.51
>20	9.9	7.0	1.60	0.96–2.65
Father smoking (cigarettes/day)				
0	64.9	60.2	1.00	
>0 to ≤20	32.9	38.0	0.80	0.59–1.09
>20	2.2	1.7	1.20	0.46–3.12
Other smokers in the home	14.2	7.2	2.23	1.37–3.63
NO_2† (ppb)				
0	24.5	39.2	1.00	
>0.5 to ≤10	18.0	43.0	0.75	0.29–1.93
>10 to ≤15	13.1	10.1	2.51	0.75–8.35
>15	44.2	7.5	10.54	3.48–31.89
Gas cooking appliance	6.6	5.2	1.33	0.68–2.58
Kerosene space heater	2.0	2.8	0.67	0.27–1.64
Mineral wool insulation‡	86.6	80.1	1.67	0.98–2.85
Urea formaldehyde foam insulation§	2.2	1.9	1.26	0.31–5.17
Fireplace	21.4	24.3	0.82	0.58–1.17
Wood stove	16.6	17.7	0.91	0.62–1.32
Year of construction of first home inhabited by the child‖				
After 1970 versus before	53.4	45.4	1.48	1.10–1.99
After 1980 versus before	20.7	14.0	1.54	1.04–2.29
Electric heating system	86.2	75.9	2.02	1.38–2.94
Central humidifier	8.5	11.8	0.67	0.42–1.07
Central air purifier	14.9	15.6	0.99	0.58–1.69
Central air conditioning	6.7	9.4	0.68	0.41–1.13
Humidifier in child's room	67.6	55.8	1.73	1.28–2.34
Wall-to-wall carpets	56.5	55.3	1.03	0.71–1.50
Dampness on windows	63.6	67.9	0.85	0.58–1.26
Occupant density <1 person/room	77.9	81.6	0.79	0.55–1.12
Pets	43.7	43.5	1.05	0.79–1.38

* Factors are defined as yes versus no if not otherwise specified.
† Based on 61 cases and 79 controls; odds ratio is unmatched.
‡ Based on 202 cases and 221 controls; odds ratio is unmatched.
§ Based on 185 cases and 216 controls; odds ratio is unmatched.
‖ Based on 365 cases and 370 controls.

nitrogen dioxide measurements. The mean ppb value for nitrogen dioxide in the 134 homes without a gas stove was 9.20 (standard deviation, 7.57); in the six homes with a gas stove, it was 17.16 (standard deviation, 8.26).

There was no notable difference between cases and controls with regard to the prevalence of other sources of chemical emissions, such as gas cooking appliances, space heaters, insulating material, fireplaces, and wood stoves. Recently built houses could be sources of more chemicals than older ones; in this study, the risk of developing asthma was greater if the first home inhabited by the child was built more recently than if it was built earlier.

Eighty percent of all study parents reported having a centralized electric heating system in the home, but more cases were exposed to it than controls; a twofold increased risk was associated with having such

a system in comparison with not having one. Among the other factors listed in table 2, only the presence of a humidifier in the child's room prior to the time of diagnosis was significantly associated with asthma.

Table 3 shows the association of other personal and socioeconomic factors with asthma. Mother's higher education was a statistically significant risk factor for asthma, and control mothers breast-fed their child slightly more often than case mothers did. Not shown in the table is the distribution of cases and controls according to language spoken at home: among case families, 85.1 percent spoke French, 3.1 percent spoke English, and 11.8 spoke another language. Among control families, these percentages were 80.5, 11.8, and 7.7, respectively. Among mothers of cases, 4.6 percent were 20 years of age or less, as compared with 1.9 percent among mothers of controls. Among case mothers, 76.1 percent were born in Québec, 6.7 percent were born in the West Indies, and 2 percent or less were born in each of 15 other regions. Among controls, 80.9 percent of mothers were from Quebec, 3.9 percent were from the West Indies, 3.7 percent were from Western Europe, and less than 2 percent were from each one of 13 other countries.

In the final conditional logistic regression model, all variables from the above tables, except the ones related to insulation materials, year of home construction, and nitrogen dioxide, were entered into the model. Variables which made an independent contribution ($p \leq 0.05$) and those which were marginally significant ($p \leq 0.10$) are shown in table 4.

Father and sibling asthma were independent risk factors for asthma, as was a past history of pneumonia. Having had a tonsillectomy was associated with an increased risk (OR = 2.83) that was marginally significant ($p \leq 0.06$). A mother's heavy smoking contributed significantly to the incidence of asthma (OR = 2.77), and the presence in the home of smokers other than the parents was associated with an odds ratio of 1.82, which did not quite reach statistical significance ($p = 0.056$). Among the other environmental factors, two were associated with increased and statistically significant odds ratios: the presence of a humidifier in the child's room (OR = 1.89) and having an electric heating system in the home (OR = 2.27). Finally, the absence of breast feeding significantly increased a child's risk of asthma. The mother's having a university education was a marginally significant risk factor ($p \leq 0.07$), whereas the presence of central air conditioning was a protective factor, likewise marginally significant ($p \leq 0.08$).

Multivariate unconditional logistic regression was carried out for the 140 subjects who had nitrogen dioxide measurements; the analysis included nitrogen dioxide and the variables retained in the final conditional model. The odds ratios for the nitrogen dioxide categories (defined as >0.5–10, >10–15, and >15 ppb, in comparison with a zero level) were 0.95 (95 percent CI 0.31–2.95), 3.85 (95 percent CI 0.92–16.09), and 19.87 (95 percent CI 4.75–83.03), respectively.

Among all study children, 52.8 percent attended day-care centers during the study period; thus, our power to detect associa-

TABLE 3. Prevalence of other personal and socioeconomic factors, matched odds ratios adjusted for allergy and eczema, and 95% confidence intervals among 457 cases diagnosed with asthma and 457 controls matched for age and area of residence, Montreal, Quebec, Canada, 1988–1990

Factor*	Cases (n = 457) (%)	Controls (n = 457) (%)	Matched odds ratio	95% confidence interval
Male	55.8	54.0	1.02	0.78–1.33
Mother has university education	23.7	17.8	1.49	1.03–2.13
Father has university education	28.2	24.1	1.21	0.87–1.68
No breast feeding	50.9	47.0	1.24	0.93–1.64

* Factors are defined as yes versus no.

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TABLE 4. Final conditional logistic regression model* for the analysis of risk factors among 457 cases diagnosed with asthma and 457 controls matched for age and area of residence, Montreal, Quebec, Canada, 1988–1990

Factor†	Odds ratio	95% confidence interval
Child is allergic	2.52	1.50–4.21
Child had eczema	1.68	1.01–2.81
Asthma in father	2.39	1.13–5.04
Asthma in siblings	2.26	1.19–4.29
Child had pneumonia	3.12	1.92–5.09
Child had tonsillectomy	2.83	0.92–8.71
Mother smoking (cigarettes/day)		
>0 to ≤20 versus 0	1.16	0.77–1.76
>20 versus 0	2.77	1.35–5.66
Other smokers in the home	1.82	0.98–3.38
Humidifier in child's room	1.89	1.30–2.74
Electric heating system	2.27	1.41–3.65
Central air conditioning	0.56	0.29–1.08
Mother has university education	1.60	0.96–2.67
No breast feeding	1.47	1.02–2.13

* All variables from tables 1–3 are present in the model (except NO_2, insulation material, and year of construction of the house), but only the odds ratios with p values ≤0.10 are shown.

† Factors are defined as yes versus no, unless otherwise specified.

tions between asthma and environmental exposures encountered in day-care centers was limited. Indeed, none of the estimated odds ratios were statistically significant. However, among cases and controls attending their first day-care center, the risk of asthma was increased when the day-care center had an electric heating system in comparison with other systems (OR = 1.32, 95 percent CI 0.81–2.16); this was also the case for the second day-care center attended (OR = 1.59, 95 percent CI 0.69–3.65).

DISCUSSION

In the literature, there appears to be no other incident density case-control study of new cases of asthma diagnosed by pediatricians among 3- and 4-year-old children. Previous studies were largely cross-sectional in design and included elementary school-aged children (generally aged 6–14 years) who, according to parental reporting, had asthma or a closely related respiratory problem such as wheezing or whistling, or had had some type of chest illness in the previous year. However, most of the potential risk factors for childhood asthma considered in the present report have been studied before. Allergies and eczema were considered as manifestations of atopy, which is strongly associated with asthma in all age groups (9). History of asthma in the family was an independent risk factor in these data, and this is generally consistent with previous findings (10–17). This was also true for pneumonia in infancy (11–13, 18, 19) and tonsillectomy (19).

Many studies have shown a statistically significant relation between passive smoking and childhood asthma (10, 15, 20, 21–28), but more have not (12–14, 16, 18, 19, 29–34). Often, a single variable was used, such as the presence or absence of parental smoking or the presence of one or two smokers, whereas in the present study, the mother's and father's levels of smoking were analyzed separately, in addition to the presence or absence of other smokers (often baby-sitters) in the home. Increased risks in this study may be due to children being younger and belonging to a narrower age group than children in most previous studies and to the physician diagnosis of disease, which is likely to have been much more uniform than that in any other study.

Reduced efficacy of lung defenses and airway injury have been postulated as mechanisms for the effects of nitrogen dioxide on respiratory health (35). From clinical studies, the short-term effects of nitrogen dioxide on asthmatics are not well characterized, although decrements in lung function have been observed. In epidemiologic studies, the focus has mainly been on exposure to nitrogen dioxide in the home environment, and the results are inconclusive. Two studies found a significant association between gas cooking appliances and the prevalence of asthma in children (21, 28), but other studies did not (12, 15, 18, 23, 24, 31–33, 36, 37). When quantitative area sampling measure-

ments of nitrogen dioxide were made in the home using diffusion tubes (22, 34, 37, 38), only once was there an association between nitrogen dioxide in the living room and childhood asthma (22). These inconsistent results are probably due to misclassification of exposure and outcome and to small study sizes (35). The probability of misclassification of residential exposure to nitrogen dioxide has recently been documented (39): It was shown to depend on the number of samples taken and on the categories used to classify results. Having a lesser number of samples was associated with substantial variability when true mean exposure was greater than 15 ppb.

Given these results, misclassification of exposure is likely to have occurred in the present study, wherein only one sample was taken on a subset of 140 subjects. However, a dose-response relation was suggested. This may be due to the use of a personal sampler s opposed to the use of a static sampler in revious studies, and to the likelihood that younger children are more susceptible to increased levels of nitrogen dioxide. In the study by Neas et al. (37), where repeated nitrogen dioxide measurements were made in different rooms with Palmes' passive diffusion tubes, the average nitrogen dioxide value for a household without a major indoor nitrogen dioxide source was 8.6 ppb (standard error, 0.2), whereas it was 23.5 ppb (standard error, 0.4) in homes where a major source existed. These results are quite comparable to those of the present study.

Other studies with different measures of home dampness have consistently found an association with asthma (28, 32, 40–43), with one exception (34). Dampness on windows was the variable used in the present study, and it was probably too vague a measure. Occupant density as a measure of crowding was not significant in this study or in many others (18, 20, 32, 33, 38). Pets are considered a definite risk factor for asthma by clinicians (44); thus, it was surprising to find that only a few studies asked about their resence (14, 28, 33, 38, 40). Moreover, ither in the present study nor in any of the previous studies was there an association between the presence of pets and the incidence of asthma. In this study, at least, the young age of the subjects may explain the negative finding, since younger children may not have had the time to be sensitized.

An interesting finding of this study is that the use of a humidifier in the child's room prior to diagnosis of asthma was strongly associated with the development of asthma. One could interpret these findings as an effect rather than a cause; that is, children with past allergies or past episodes of infection have had previous medical care, and their parents may have been urged to buy a humidifier. Thus, the humidifier use would simply be a proxy for respiratory symptoms that were not yet recognized as asthma. However, we adjusted in the analyses for personal susceptibility, past infections, and family history. Moreover, in the subgroup of 507 children without any allergies or past infections, the unmatched odds ratio for asthma associated with having a humidifier in the child's room was 1.57 (95 percent CI 1.07–2.31).

In another Canadian study, Dekker et al. (28) reported an increased odds ratio associated with the use of a humidifier in the home, but it seems that this variable was use of a central humidifier. In Montreal, winters are long and very cold, and heating systems work continuously; as a result, indoor air is often dry. There is a belief among the lay public that some humidity is necessary for avoiding respiratory illness in children. We can only speculate about the mechanism by which a humidifier may be a risk factor for the development of asthma. Growth of biologic agents in the ducts of the humidifier is one possibility (45, 46). It is also possible that a humidifier could increase the level of house dust mites implicated in the development of asthma (47), since the conditions for their growth are similar to those for fungi (48). However, the outdoor climatic conditions favoring the growth of mites are high humidity and moderate temperature (49), and these conditions are rarely met in Montreal.

Although an electric heating system was never found to be significant in any of the few studies that have considered it as a potential risk factor for childhood asthma (21,

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24, 28, 33, 40), it was an independent risk factor in this study. Unfortunately, sample size became too small to determine whether the delivery of heat through forced air, radiant heat, or water radiators modified that effect.

It is not clear why the present study did not find that boys were at increased risk of asthma because many previous studies did (12, 19, 22, 25, 50), although not all (20). Finally, contrary to most studies (14, 19, 25, 40, 50, 51), the present study showed an association between asthma and breast feeding. Only one other study reported that breast feeding was a protective factor (19). The younger age of our study subjects is a likely explanation for these discrepancies. Indeed, the protective effect may not last beyond early infancy.

Misclassification of outcome is a potential concern in most studies of childhood asthma, including this one. However, had many cases not been asthmatics and many controls underdiagnosed, it is unlikely that the study would have shown increased risks for markers of atopy, family history, and previous infections. Potential selection bias needs to be addressed. Controls living in the same census tract were considered a reasonable choice for the study base. However, only families who still resided at the address given in the files were sampled as controls. If the studied factors were associated with mobility, then the proportion of controls exposed to these factors would have been underestimated in this study. There are some indications that this was not the case. For instance, a recent national survey (52) showed that among Quebec women aged 20–44 years in 1986, 37.5 percent were regular smokers, which is identical to the proportion found among control mothers in this study. In addition, in 1983, the prevalence of asthma in 3- and 7-year-old children in Montreal was estimated to be 6.4 percent (53), which is close to the 5.4 percent found among controls in the present study. We also note that socioeconomic factors, which may be associated with mobility, were controlled for in the analysis.

In conclusion, this incident density case-control study showed that even after accounting for personal susceptibility, family history, past infections, and factors related to the indoor environment contribute significantly to the incidence of asthma. For future studies to have a greater impact on public health, it will be necessary to assess exposure-response relations and to relate findings to suggested protective standards. Obtaining reliable quantitative measurements will be the challenge to future studies.

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The authors of this study measured urinary cotinine levels in 199 children with asthma. One-hundred-forty-five children also underwent pulmonary function testing. Parents of the children were asked to fill out questionnaires regarding the children's exposure to parental smoking. The authors reported that acute exacerbations of asthma increased with exposure to ETS, whether the exposure was reported by a parent or based on cotinine level in the urine. The authors reported relative risks of 1.8 [95% CI: 1.4-2.2] for reported exposure by parents and 1.7 [95% CI: 1.4-2.1] for exposure based on cotinine level. The authors reported that pulmonary function performance also decreased as the estimated exposure increased. The authors concluded that "measurement of urine cotinine levels provides further evidence of an association between exposure to environmental tobacco smoke and pulmonary morbidity in children with asthma."

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ASSOCIATION BETWEEN EXPOSURE TO ENVIRONMENTAL TOBACCO SMOKE AND EXACERBATIONS OF ASTHMA IN CHILDREN

BARBARA A. CHILMONCZYK, M.D., LUIS M. SALMUN, M.D., KEITH N. MEGATHLIN, M.D., LOUIS M. NEVEUX, B.S., GLENN E. PALOMAKI, B.S., GEORGE J. KNIGHT, PH.D., ANDREA J. PULKKINEN, M.S., AND JAMES E. HADDOW, M.D.

Abstract *Background.* Exposure to environmental tobacco smoke, as reported by parents, has been linked to diminished pulmonary function and more frequent exacerbations of asthma in children with the disease. Further insight into this association might be gained by using urine cotinine levels to measure actual exposure.

Methods. We measured urine cotinine levels in 199 children with asthma; 145 also underwent pulmonary-function studies. A parent answered questions about each child's exposure to environmental tobacco smoke. Acute exacerbations of asthma during the preceding year were documented through blinded review of medical records. Possible confounding factors were accounted for by the use of multivariate analysis and by comparisons of serum theophylline levels in exposed and unexposed children.

Results. The median urine cotinine levels were 5.6 ng per milliliter in the 116 children reported not to have been exposed to tobacco smoke, 13.1 ng per milliliter in the 53 children exposed to cigarette smoking by the mother or other persons, and 55.8 ng per milliliter in the 30 children exposed to cigarette smoking by the mother and other persons. Acute exacerbations of asthma increased with exposure, whether such exposure was reported by a parent or identified on the basis of the cotinine level; the relative risks for the highest as compared with the lowest exposure category were 1.8 (95 percent confidence interval, 1.4 to 2.2) for reported exposure and 1.7 (95 percent confidence interval, 1.4 to 2.1) for exposure indicated by cotinine levels. The forced expiratory volume in one second (FEV_1), the forced expiratory flow between 25 and 75 percent of vital capacity, and the ratio of FEV_1 to forced vital capacity also decreased with increases in both measures of exposure.

Conclusions. Measurement of urine cotinine levels provides further evidence of an association between exposure to environmental tobacco smoke and pulmonary morbidity in children with asthma. These data emphasize the need for systematic, persistent efforts to stop the exposure of children with asthma to environmental tobacco smoke. (N Engl J Med 1993;328:1665-9.)

ASTHMA is the most common chronic lung disorder in children; it affects approximately 2 million to 5 million children in the United States. Exposure to environmental tobacco smoke has been reported to affect children with asthma adversely in a variety of ways; its effects include a decrease in pulmonary function,[1-3] an increase in airway reactivity,[1-6] and an increase in the frequency of visits to the emergency room for treatment of acute exacerbations of asthma.[7] Three studies have suggested that children exposed to environmental tobacco smoke may have a higher-than-average risk of asthma.[8-10]

To date, the published studies that have examined the consequences of exposure to environmental tobacco smoke in children with asthma have relied exclusively on parents' reports of their smoking habits. Even reliable parental reports of exposure to environmental tobacco smoke could be relatively inaccurate, however, as a measure of children's actual inhalation of such smoke. Although this inaccuracy is not likely to interfere with analyses comparing exposed and unexposed groups, it could make it difficult to detect a dose–response relation. If cotinine measurements were found to be consistent with parental reports of children's exposure to environmental tobacco smoke, this measurement could provide additional validation for published studies that have linked reported exposure to pulmonary morbidity. Moreover, if a dose–response relation were identified between morbidity and cotinine levels, this relation would strengthen the argument in favor of causality and lessen the possibility that exposure to environmental tobacco smoke serves only as a marker for other environmental or socioeconomic factors.

We used urine cotinine levels in addition to parental reports to examine these questions further in a population of children who were receiving ongoing specialized care for asthma. Cotinine, a metabolic derivative of nicotine, is excreted in the urine and serves as an accurate, short-term quantitative measure of the intake of tobacco smoke. The circulating half-life of cotinine is approximately 24 hours.[11,12] In this study, pulmonary-function measurements and acute exacerbations of asthma were the health-related end points analyzed in relation to both parental reports of exposure to environmental tobacco smoke and urine cotinine concentrations.

METHODS

Study Population

From February 20 through May 9, 1992, 204 children with asthma (age, 8 months to 13 years) and the parents who accompanied them to routine visits at a large allergy–asthma practice in Portland, Maine, were asked by the office staff whether they were willing to take part in a clinical study. The study had been approved by the institutional review boards of the Foundation for Blood Research and the Maine Medical Center. A total of 199 pairs of children and parents agreed to participate, and the parents gave written consent. At enrollment, each parent filled out a questionnaire, and a urine sample was obtained from each child. In addition to obtaining demographic data about the child, the questionnaire sought information on the following: the parents' occupations and years of education completed; the number of people in the household; the age at which the child was given a diagnosis of asthma; the child's current

From the Foundation for Blood Research, Scarborough, Me. (B.A.C., L.M.N., G.E.P., G.J.K., A.J.P., J.E.H.); and the Maine Medical Center, Portland (B.A.C., L.M.S., K.N.M.). Address reprint requests to Dr. Haddow at the Foundation for Blood Research, P.O. Box 190, Scarborough, ME 04070-0190.

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medication status; the child's school status; use of day care outside of the home; smoking at the day-care site, including an estimate of the amount; the current smoking status of the accompanying parent, including the number of cigarettes smoked per day and the estimated number of hours per week of smoking in the home; and the current smoking status of all others in the household, including the estimated number of cigarettes (or cigars or pipes) smoked per day.

Pulmonary-function tests were also performed at enrollment in the 145 children who were capable of performing the forced expiratory maneuver. All the children's medical records were reviewed in a blinded fashion to determine the number of acute exacerbations of asthma during the 12 months before enrollment and to obtain information about use of medications. Using published guidelines from the National Heart, Lung, and Blood Institute,[13] we classified asthma as mild in 47 of the children (23.6 percent), moderately severe in 145 (72.9 percent), and severe in 7 (3.5 percent).

Urine Cotinine and Creatinine Analyses

Urine samples were frozen and stored to be analyzed in batches. The measurement of cotinine was performed with use of an iodine-125 competitive radioimmunoassay, the details of which have been previously reported.[14] Creatinine was also measured in each sample, with use of a commercially available kit (Sigma Diagnostics, St. Louis).

Statistical Analysis

In an earlier study,[15] urine cotinine levels were found to be consistent with exposure to environmental tobacco smoke at a level of 10 ng per milliliter (57 nmol per liter) or higher. Continuous variables were compared by t-test after appropriate transformations of the data. Categorical variables were compared with the chi-square test. Cotinine levels were corrected for the concentration of the urine by fitting the relation between the log cotinine level and the log creatinine level,[16] with use of a second-order curve. The dose–response relation between the two measures of exposure to environmental tobacco smoke and the results of the four pulmonary-function tests was assumed to be linear. Stepwise multivariate linear-regression analysis was, therefore, used to estimate the extent of the change in pulmonary function associated with increasing levels of exposure. In this analysis we controlled for the mother's age and education level and the child's age, sex, and attendance at day care. To allow a direct comparison between reported exposure and cotinine levels, the cotinine cutoff points were chosen to include the same number of children in each category of cotinine intake as dictated by the reported exposure categories. All analyses were performed with the BMDP statistical package.[17]

Results

Table 1 compares selected characteristics of the study population according to the presence or absence of reported exposure to environmental tobacco smoke. According to parental reports, 83 (42 percent) of the children were exposed to environmental tobacco smoke. Boys predominated in both the nonexposed and the exposed categories. In households where exposure to environmental tobacco smoke was reported, the average age of the mothers was younger, they had fewer years of education, and children's enrollment in day care was more frequent. Urine cotinine measurements were significantly higher when exposure to environmental tobacco smoke was reported.

Figure 1 shows urine cotinine concentrations in relation to exposure to environmental tobacco smoke as reported by the parents. The median cotinine concentrations increased monotonically in the three defined categories (no exposure to environmental tobacco

Table 1. Characteristics of Children with Asthma, According to Parental Reports of Exposure to Environmental Tobacco Smoke.*

Characteristic	No Exposure	Exposure	P Value
No. of children	116	83	—
Percent boys	75	67	0.3
Percent in school	82.6	80.7	0.7
Percent in day care	18.1	49.4	<0.001
Age at enrollment (yr)	7.4±2.8	7.6±2.9	0.7
Age at diagnosis (yr)	4.0±2.8	4.3±2.6	0.6
Mother's age at enrollment (yr)	35.4±4.5	33.1±6.3	0.01
Mother's education (yr)	15.0±2.4	13.0±1.8	<0.001
No. of people in household	4.2±0.9	4.1±1.1	0.6
Urine cotinine level (ng/ml)	5.6±0.33†	23.3±0.44†	<0.001

*Plus–minus values are means ±SD, unless otherwise noted.

†The median ±SD of the $\log_{10}$ cotinine level. To convert values for cotinine to nanomoles per liter, multiply by 5.7.

smoke, exposure to smoking by the mother or other persons, and exposure to smoking by the mother and other persons). Of the 116 cotinine measurements in the group with no reported exposure to environmental tobacco smoke, 100 were below 10 ng per milliliter, a level previously established as consistent with minimal exposure; except for 1 cotinine measurement of 40 ng per milliliter (228 nmol per liter), the highest level in this group was 20 ng per milliliter (114 nmol per liter). Of the 30 cotinine measurements in the group with the highest reported level of exposure (smoking by the mother and other persons), all were above 10 ng per milliliter, and all but 3 were above 20 ng per

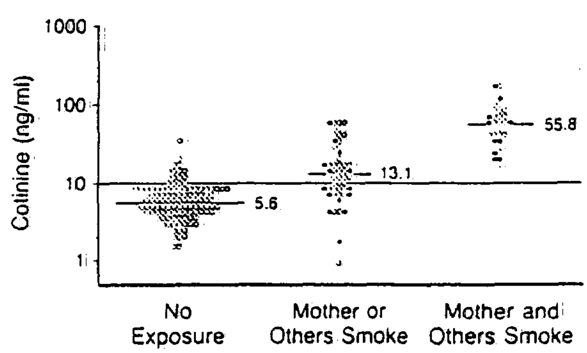

Figure 1. Relation between Reported Exposure to Environmental Tobacco Smoke and Urine Cotinine Concentrations in 199 Children with Asthma.

Urine cotinine concentrations (corrected for the creatinine concentration) are represented on a logarithmic scale. Three mutually exclusive levels of exposure to environmental tobacco smoke reported by parents are shown. Solid circles identify children in day-care settings in which exposure to environmental tobacco smoke was reported. The horizontal line at 10 ng of cotinine per milliliter is an arbitrary demarcation point, above which exposure to environmental tobacco smoke was considered substantial. Median cotinine levels are indicated for the three exposure levels. To convert values for cotinine to nanomoles per liter, multiply by 5.7.

milliliter. Cotinine measurements in the intermediate-exposure group (smoking by the mother or other persons) were less consistent, indicating more variable intake of tobacco smoke. Reported exposure to environmental tobacco smoke in the day-care setting did not add measurably to the children's cotinine levels, over and above household exposure. Table 2 shows the extent to which parental reports of exposure to environmental tobacco smoke correlated with measurements of cotinine in urine. Overall, when the cutoff level of 10 ng per milliliter was used for urine cotinine, the two methods agreed for 164 of the 199 children.

Table 3 demonstrates that, as reported exposure to environmental tobacco smoke increases, acute exacerbations of asthma increase and pulmonary function decreases. A monotonic pattern of increased morbidity was found for acute exacerbations of asthma but not for the measures of pulmonary function. The observed changes in the four measures of morbidity due to asthma for each increase in the category of exposure to environmental tobacco smoke were initially analyzed with use of simple linear regression analysis (observed) and then further analyzed with use of a multivariate linear regression model that included the mother's age and education level and the child's age, sex, and day-care attendance (adjusted). The 95 percent confidence intervals for the adjusted estimates indicate that three of the four measures of morbidity were significantly worse with increasing exposure to environmental tobacco smoke. For the number of acute exacerbations in the previous year, the adjusted relative risk for the highest as compared with the lowest exposure category was 1.8 (95 percent confidence interval, 1.4 to 2.2).

Table 4 repeats the analyses in Table 3, but in this case we used urine cotinine measurements, rather than parental reports, to measure the intake of environmental tobacco smoke. The same trends were found as in Table 3, but a monotonic pattern was found for both the increase in acute exacerbations of asthma and the decrease in the measures of pulmonary function. After adjustment for potential confounders, the 95 percent confidence intervals for three of the four measures indicated that significantly increased morbidity due to asthma was associated with the actual intake of environmental tobacco smoke. The relative risk for the number of acute exacerbations of asthma in the previous year in the highest as compared with the lowest intake category was 1.7 (95 percent confidence interval, 1.4 to 2.1), after adjustment for possible confounders.

The extent to which the information provided by reported exposure to environmental tobacco smoke overlaps with that provided by cotinine measurements can be examined by testing the effect of adding one of these measures (cotinine levels or reported exposure) to a multivariate model that already contains the other, along with possible confounders. When reported exposure was tested in relation to acute exacerbations of asthma in this multivariate model, it added significant predictive power ($F = 5.99$, $P = 0.02$), whereas cotinine levels did not ($F = 0.05$, $P = 0.8$). In relation to pulmonary function, neither cotinine levels nor reported exposure added significant predictive power to a model already containing the other (for reported exposure: $F = 0.35$, $P = 0.6$ for the relation to the forced expiratory volume in one second [FEV_1]; $F = 0.48$, $P = 0.5$ for the relation to the forced expiratory flow between 25 and 75 percent of vital capacity [FEF_{25-75}]; and $F = 1.01$, $P = 0.3$ for the relation to the ratio of FEV_1 to forced vital capacity [FVC]; for cotinine measurements: $F = 2.82$, $P = 0.1$ for the relation to FEV_1; $F = 1.73$, $P = 0.2$ for the relation to FEF_{25-75}; and $F = 2.01$, $P = 0.2$ for the relation to FEV_1:FVC).

Theophylline was prescribed for 104 of the 199 children with asthma during the year before enrollment, including 45 (54 percent) of the 83 exposed to environmental tobacco smoke and 59 (51 percent) of the 116 not exposed. Serum theophylline levels were available for 27 of the exposed children and

Table 2. Agreement between Urine Cotinine Levels and Reported Exposure to Environmental Tobacco Smoke in Children with Asthma.*

Cotinine Level	Exposure	No Exposure	Total
≥10 ng/ml	64	16	80
<10 ng/ml	19	100	119
Total	83	116	199

*To convert values for cotinine to nanomoles per liter, multiply by 5.7.

Table 3. Current Pulmonary Function and Number of Acute Exacerbations of Asthma during the 12 Months before Enrollment, According to Reported Exposure to Environmental Tobacco Smoke.*

Variable	No Exposure	Mother or Others Smoke	Mother and Others Smoke	Change per Category of Increasing Exposure	
				Observed	Adjusted (95% CI)†
No. of children‡	166/83	53/41	30/21	—	—
No. of acute exacerbations	2.2±2.0	2.5±1.6	3.9±2.7	0.75	0.83 (0.39 to 1.26)
FEV_1 (%)	109.3±20.7	102.4±26.0	102.2±17.9	−4.3	−2.3 (−7.9 to 3.3)
FEF_{25-75} (%)	85.4±26.7	71.8±30.6	73.6±19.3	−7.6	−8.2 (−15.4 to −1.0)
Ratio of FEV_1 to FVC (×100)	83.7±7.6	79.4±8.4	80.0±7.0	−2.4	−3.1 (−5.0 to −1.0)

*Plus–minus values are means ±SD. FEV_1 denotes forced expiratory volume in one second, FEF_{25-75} forced expiratory flow between 25 and 75 percent of vital capacity, and FVC forced vital capacity.

†Adjusted for the mother's age and education level and the child's age, sex, and day-care attendance. CI denotes confidence interval.

‡The number available for the analysis of acute episodes of asthma, followed by the number available for the analysis of pulmonary-function studies.

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Table 4. Current Pulmonary Function and Number of Acute Exacerbations of Asthma during the 12 Months before Enrollment, According to Intake of Environmental Tobacco Smoke as Defined by the Urine Cotinine Level.*

Variable	Cotinine			Change per Category of Increasing Intake	
	<10 ng/ml	10–39 ng/ml	>39 ng/ml	Observed	Adjusted (95% CI)†
No. of children‡	116/83	53/41	30/21	—	—
No. of acute exacerbations	2.1±1.9	2.8±1.8	3.6±2.9	0.80	0.63 (0.10 to 1.07)
FEV_1 (%)	108.8±20.3	105.2±24.7	98.5±22.3	−4.8	−4.7 (−9.9 to 0.5)
FEF_{25-75} (%)	85.4±26.8	74.9±28.8	67.3±22.8	−9.4	−8.5 (−15.2 to −1.9)
Ratio of FEV_1 to FVC (×100)	83.5±7.5	81.2±8.1	77.5±8.0	−2.8	−3.0 (−4.9 to −1.1)

*Plus–minus values are means ±SD. FEV_1 denotes forced expiratory volume in one second, FEF_{25-75} forced expiratory flow between 25 and 75 percent of vital capacity, and FVC forced vital capacity. Urine cotinine concentrations have been adjusted for the creatinine concentration. To convert values for cotinine to nanomoles per liter, multiply by 5.7.

†Adjusted for the mother's age and education level and the child's age, sex, and day-care attendance. CI denotes confidence interval.

‡The number available for the analysis of acute episodes of asthma, followed by the number available for the analysis of pulmonary-function studies.

36 of the unexposed children. When more than one measurement was available for a given child during the preceding year, only the first was included in the analysis. Measurable theophylline levels were present in all 63 of the children. The mean serum theophylline levels of 11.37 μg per milliliter (62.5 μmol per liter) in the exposed children and 11.42 μg per milliliter (62.8 μmol per liter) in the unexposed children were similar ($t = -0.04$, $P = 0.97$).

Discussion

Data from this study provide further validation of published reports that exposure to environmental tobacco smoke adversely affects the health of children with asthma.[1-9,18] Furthermore, the cotinine measurements in this study group provide information not previously available: parental reports indicating no exposure to environmental tobacco smoke were consistent with cotinine measurements 86 percent of the time, and parental reports indicating exposure were consistent with measured levels 77 percent of the time. Discrepancies between parental reports and cotinine measurements might be explained by incomplete knowledge of exposure, on the one hand, or variability in environmental conditions leading to diminished inhalation of environmental tobacco smoke, on the other. Purposeful misreporting of smoking habits is unusual.[11,12] Cotinine is a measure of actual recent intake of smoke from cigarette products and, as such, will not always agree with the reported smoking habits of nearby persons.

Significant increases in the frequency of acute exacerbations of asthma were found whether exposure to environmental tobacco smoke was identified on the basis of parental reports or urine cotinine levels, and monotonic dose–response patterns were evident with both methods. Significant reductions in pulmonary function were also found, whether exposure to environmental tobacco smoke was assessed on the basis of parental report or cotinine level, and linear dose–response patterns were evident when the exposure was defined by the cotinine level. The linear dose–response patterns provide further evidence of a causal relation between exposure to environmental tobacco smoke and pulmonary morbidity in children with asthma.

Some or all of the morbidity associated with exposure to environmental tobacco smoke may be attributable to the differences between the exposed and unexposed populations (Table 1). This possible confounding was taken into account in the multivariate analyses summarized in Tables 3 and 4. The observed and adjusted values for each of the variables measured were not very different, indicating that, at most, only a small proportion of the observed relation can be explained by confounding.

The theophylline levels in a subgroup of the study population served as a measure of compliance; they provide evidence that the exposed and unexposed children followed medical advice similarly. These levels were obtained in a nonstandardized fashion as part of routine management, and in nearly all instances the children had been treated with theophylline for a considerable period of time.

Our findings are consistent with the results of studies of infants and children without asthma, in which more frequent respiratory infections and diminished pulmonary function were found to be associated with reported exposure to environmental tobacco smoke.[19-27] Dose–response relations have been identified between the degree of exposure to environmental tobacco smoke reported by parents and pulmonary function in one cohort of children with asthma[1,2] and in several studies of children without asthma.[22-24,27]

The urine cotinine levels in the current study indicate that parental reports are reliable when used to screen for exposure to environmental tobacco smoke in children with asthma. These observations provide further support for the results of published studies that rely on parental reports in examining the relation of exposure to environmental tobacco smoke and pulmonary morbidity. Urine cotinine levels can provide additional information when exposure to environmental tobacco smoke is reported, both in assessing the degree of actual intake (with its attendant risks) and in monitoring efforts to reduce exposure. The evidence that environmental tobacco smoke has a causal role in asthma-related morbidity is sufficiently strong, and the adverse pulmonary effects are sufficiently great, that systematic efforts to reduce inhalation of environmental tobacco smoke are warranted for children with asthma.

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EXPERIMENTAL STUDIES ON ACUTE EFFECTS OF PASSIVE SMOKING IN ASTHMA

H. Magnussen

Krankenhaus Großhansdorf, Zentrum für Pneumologie und Thoraxchirurgie, D-2070 Großhansdorf, Tel.: +49 (4102) 601150, Fax: +49 (4102) 601245

Patients with asthma often complain of respiratory symptoms during or after passive smoking. Experimental studies on the effects of short-term passive smoking have been performed in adults but not in children; their results are heterogeneous and some of them show deficiencies of their study design. In a series of controlled exposure studies we investigated the occurrence and degree of acute effects of short-term passive smoking in adults and children with asthma. Throughout all studies we used a constant cigarette smoke concentration of 20 ppm carbon monoxide.

In the first study 24 adult patients with mild bronchial asthma and 16 healthy subjects were enrolled. Subjects breathed cigarette smoke or room air while sitting at rest for one hour. Lung function was measured before and after exposure, and airway responsiveness to inhaled methacholine was determined within one hour after exposure. As compared to room air, lung function parameters did not change significantly and airway responsiveness was not altered after passive smoking.

As it seemed reasonable to expect a more pronounced airway response to air pollutants in children than in adults, we then studied 11 children with mild bronchial asthma while using an analogous experimental protocol. However, similarly as seen in the adults, lung function and airway responsiveness to inhaled histamine were not affected by one hour of passive smoking in these children.

The next study was designed to investigate the effects of cigarette smoke during vs after exposure and to compare the effects observed at resting ventilation with those observed at increased ventilation rate. Thirteen children with exercise-induced asthma participated in this study. They breathed either cigarette smoke or room air for one hour and exercised on a bicycle ergometer during the last six minutes of exposure. Mean forced expiratory volume in one second, as a measure of lung function, decreased by about 5% during passive smoking as compared to room air. This effect could be attributed to three smoke-sensitive children and disappeared during and after exercise testing.

Most patients with bronchial asthma show an increase in symptoms, an impairment of lung function and an enhancement of airway responsiveness during night compared to daytime. Thus, in a further study we investigated the effects of passive smoking in the evening on the course of lung function and airway responsiveness until the next morning. Seventeen subjects with mild bronchial asthma were exposed to cigarette smoke or room air for three hours at rest. On the average, lung function did not change during passive smoking but demonstrated small impairments at 03.00 a.m. in the night and 07.00 a.m. in the next morning. Similarly, airway responsiveness to methacholine showed a tendency towards increased values at these times.

From these studies we conclude that individual patients with asthma can show a temporary impairment of lung function during or several hours after passive smoking. It is noteworthy that it is difficult to detect smoke-sensitive subjects reliably, since there is no obvious correlation between measured changes of functional parameters and acute or anamnestic symptoms due to passive smoking.

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IS PASSIVE SMOKING A CAUSE OF ASTHMA IN CHILDHOOD?

R. Ehrlich[1], M. Kattan[2], D.E. Lilienfeld[3]

[1]Department of Community Health, University of Cape Town Medical School, Cape Town, South Africa; [2]Division of Environmental and Occupational Medicine, Department of Community Medicine; [3]Jack and Lucy Clark Department of Pediatrics, Mount Sinai School of Medicine, New York, USA

Abstract

There is growing evidence, although not wholly consistent, that maternal smoking is a risk factor for asthma and wheezing illness in childhood. The epidemiological evidence for this association is reviewed including considerations of study design, misclassification and confounding. While the timing and mechanism of this effect, whether prenatal or postnatal, are not yet known, it is concluded that there is sufficient evidence for public health purposes to target maternal smoking as a modifiable risk factor for wheezing illness in childhood.

Key words: Environmental tobacco smoke, passive smoking, epidemiology, asthma, child health

Introduction

The association between passive smoking and childhood asthma is currently the object of considerable and growing interest. Earlier reviews of the subject, while providing good evidence for an association between maternal smoking and lower respiratory illness in children under two years of age [1–7], were unable to deduce an association between passive smoking and asthma or wheezing in childhood with any confidence, in view of a number of negative or equivocal studies [8–13].

However, in the light of reports of an increase in asthma prevalence, hospital admissions and mortality among young people in a number of countries in recent years [14–19], indoor air pollutants such as passive smoking have been identified as potential contributors to such trends [19]. A possible causal association between passive smoking and childhood asthma would thus be of considerable public health importance.

Such an association has biological plausibility, especially if one includes the effects of smoking on the foetus *in utero* under the broad heading of passive smoking. *In utero* effects of nicotine and maternal smoking on the foetal rodent respiratory system have been produced experimentally [20,21], while increased IgE levels have been reported in the newborns of smoking mothers [22]. Inhalational effects on young children leading to an asthmatic response can also be postulated, as environmental tobacco smoke (ETS) may initiate inflammatory or immunological processes in airway walls, for example by increasing epithelial permeability [23]. Episodic airway narrowing in response to allergens, irritants or infection may be

Address correspondence to Dr R.I. Ehrlich, Department of Community Health, University of Cape Town Medical School, Observatory 7925, South Africa. *(Accepted for publication 30.1.93.)*

mediated by an increased prevalence or tendency to non-specific bronchial hyperresponsiveness, IgE levels or atopy [24,25] or mucus hypersecretion associated with exposure to ETS [26].

Although increases in bronchial hyperresponsiveness [27,28] and IgE levels [29,30] have been shown among active smokers, active smoking does not appear to be a strong predictor of asthma [31,32]. However, asthmatics may be less likely to smoke, or more likely to quit smoking, thus obscuring an underlying aetiological association.

The number of epidemiological studies of the association between passive smoking and asthma and wheezing in children is growing and the aim of this review is to re-examine the epidemiological evidence. Because of underdiagnosis of asthma [33] and the difficulties of defining asthma for epidemiological purposes [34], wheezing [35] as well as non-specific bronchial hyperresponsiveness are included as outcomes of interest, although they may lack some specificity for clinical asthma. For purposes of exposition, the epidemiological studies are divided according to the type of population studied, *viz.* general population studies and studies of asthmatics using health services. These in turn are further grouped according to study design.

General population studies

Prospective general population studies offer the advantages of establishing the parental smoking habit in advance of the disease, including the opportunity for repeated measurement of smoking, and for reducing recall bias by parents of asthmatic or wheezing children. There are now a fair number of large prospective studies which have investigated the assocation between passive smoking and asthma or wheezing.

Early studies in this category found no association between parental smoking and asthma [12,13] or an association with wheezing only if both parents smoked [8]. More recent prospective studies that have separated maternal smoking from other sources of passive smoking have generally been able to show an effect, although again not in all subgroups examined. Thus, an association has been demonstrable in various ways for wheezing illness but not asthma [36,37], among children of less educated mothers only [38], or only in younger children [39]. Studies of wheezing illness in infant [40,41] have strengthened other finding regarding early lower respiratory tract illnes [42,43], by showing that maternal smoking increases the risk of such wheezing episodes

Cross-sectional general population stud ies are less onerous and expensive to moun than prospective studies and, therefore, mor numerous, but suffer the disadvantage c collecting symptom or illness informatio contemporaneously with smoking data Parents of symptomatic children may alt their smoking habits or may report suc habits differently from parents of asympto matic children. Further, unless smokin habits are constant or the aetiological impa ongoing, current smoking may be a poo indicator of a relevant causal exposure occu ring some years earlier.

As with prospective studies, there h been considerable variability of results amo those cross-sectional studies that did n distinguish between maternal and oth sources of smoking. Some such studies ha been clearly positive [44,45] but a numb have reported no association betwe parental smoking and asthma or whee [10,11,46,47]. Others have been margin positive [48], have demonstrated association with wheeze but not asth [49,50], in one sex only [51,52], amo English but not Scottish children [52] or c if a co-factor such as dampness at home v also present [53].

In those cross-sectional studies wi examined maternal smoking as a sepa variable, the evidence is more strongly c sistent for an association with asthma [54–57] and for wheezing [58]. In addit Ekwo *et al.* [59] found an association tween maternal smoking and 'wheezing colds' but not 'wheezing without colds'. Martinez *et al.* [24] reported an associ with bronchial hyperresponsiveness am boys but not girls. Only Schenker *et al.*

found no relationship between maternal smoking and asthma or wheezing, while O'Connor *et al.* [60] could demonstrate an association of maternal smoking with bronchial hyperresponsiveness only in the subgroup of asthmatic children in their sample.

Studies of asthmatics

Asthmatic populations may be drawn from a hospital or clinic, or identified as part of a general population study. Case control studies, in which asthmatics are compared to some non-asthmatic group, test the same hypothesis as the studies in the previous section, *i.e.* whether asthma occurrence is associated with passive smoking. Studies of asthmatics without a control group, on the other hand, investigate whether passive smoking aggravates the asthmatic state.

There have been a number of case-control studies in which the cases were drawn from a clinic or hospital [61–65]. Of these, three have found a positive association between some measure of parental smoking and asthma [62–64]. These studies have generally been small, and must be interpreted carefully because of the impact of various biases which may operate through differences between cases and controls in the way they are selected, in the manner they are questioned, and in the accuracy of recall of smoking and of potential confounders. For example, of the above studies, three [61–63] made no adjustment for confounders.

Of interest is that three of the hospital-based case-control studies used urinary cotinine as a biomarker of exposure: two found significant differences in cotinine levels between asthmatics and controls [63,64] and one no difference [65]. While cotinine is a potentially useful marker of passive smoking in asthma studies, a single reading appears to be subject to a variety of influences other than the reported level of passive smoking in the home, and there are a number of methodological questions regarding its use which remain to be resolved [64,66,67].

There have been few studies of the effect of maternal smoking among diagnosed asthmatics. Murray and Morrison [68–70] have shown that asthmatic children whose mothers smoke have worse symptoms and lung function and greater bronchial hyperresponsiveness than asthmatic children whose mothers do not smoke. Corroboration of these findings has come from general population studies in which, among the subgroup of children with parent-reported asthma, bronchial hyperresponsiveness was increased if there was a smoking mother or parent [24,60,71]. Asthmatics exposed to smoking at home also seem to have more frequent visits to the emergency room than those without such exposure [72].

Discussion

Despite inconsistency among the studies reviewed, a coherent pattern is emerging. In particular, studies which have been able to separate out maternal smoking have been more consistently positive than those that did not make this distinction. Further, among the studies which quantified maternal smoking [13,36,40,55,58,69], nearly all have been able to show some exposure-response relationship between maternal smoking and some measure of asthma or wheeze.

The relative risk or odds ratio in the larger studies which controlled to some degree for confounding has been modest, of the order of 1.5 [36,39,54,57,58]. In contrast, most studies have failed to show an effect of paternal smoking.

This maternal predominance may reflect *in utero* influences, the child's inhalational exposure to ETS from maternal sources, or both. It is difficult to separate these influences epidemiologically as mothers who smoke in pregnancy can be expected to continue after the child is born.

Measurement of lung function in neonates has allowed the application of the tools of epidemiology to investigate the effect of *in utero* (or at least very early postnatal) exposure. Diminished lung function [73] and increased non-specific bronchial hyperresponsiveness [74] have been shown in infants of mothers who smoked in pregnancy. Further, early lung function decrement has been shown to predict the likelihood of early

wheezing lower respiratory illness [75,76]. Taken with evidence that early lower respiratory infection, particularly bronchiolitis, is a predictor of later wheezing and asthma [77–80], this may be one pathway for the impact of exposure *in utero* or in early neonatal life in the aetiology of asthma. There is also limited evidence of immunological effects *in utero*: there is one report of elevated IgE levels in the cord blood of neonates of smoking mothers [22].

There is probably more than one mechanism underlying the relationship between maternal smoking and asthma, however. The maternal predominance may reflect the closer association between smoking mothers and young children in the home environment, and the greater role of maternal smoking in the ETS exposure of the child. This has been corroborated by studies using cotinine as a marker of exposure, which have been able to show a greater contribution to nicotine absorption by the child if the mother was the only smoker compared to that of lone paternal smoking [81–84].

In general, the evidence for an effect of passive smoking on wheezing and other lower respiratory illness is more consistent for children under two years of age than that for older children. To the extent that this is due to postnatal exposure it suggests that such exposure in the first few years of childhood may be more critical, or alternatively more intense, than later exposure to maternal ETS. However, there is evidence for at least some ongoing effect of maternal smoking on the incidence of wheezing [37] or asthma severity [70] in older children.

There is also consistent evidence that among children already asthmatic, maternal smoking is associated with more severe asthma [68–70], more frequent visits to the emergency room [72] and greater bronchial hyperresponsiveness [24,60,68–71].

Regarding the timing of the effect, Frischer *et al.* [71] found reported maternal smoking in infancy to be more closely associated with bronchial hyperresponsiveness among eight-year-old asthmatics than was current maternal smoking. In contrast, in Murray's report [69], seasonal variation in bronchial hyperresponsiveness seemed to be related to the degree of contemporaneous exposure to maternal smoking.

Although commonly held to be an irritant for some asthmatics and a modifiable cause of asthma attacks [61] there has been little direct testing of the hypothesis that passive smoking triggers asthmatic attacks in children. Clinical laboratory studies of children [85] and young adults have been inconsistent [86–90]. Objective hypersensitivity to tobacco antigens has also not been shown to be associated with eye, nasal and bronchial symptoms among individuals reporting themselves to be sensitive to ETS [91].

Despite the emerging evidence concerning the importance of maternal smoking, variation remains among study findings, and this is likely to continue. Part of this variation between studies is due to the difficulties of measuring accurately the child's true dose of smoke exposure. Furthermore, ETS is a complex mixture of agents [92], any or a number of which may be implicated.

However, misclassification of the child's 'true' exposure is unlikely to produce spurious positive findings. In general, such misclassification will be random, i.e. uninfluenced by whether the child has asthma or not and will move the study findings in the direction of no association. Non-random misclassification could conceivably arise in certain circumstances, for example, if parents of asthmatics deny their smoking. The effect of this, however, will also make it more difficult to observe a positive association.

Similarly, misclassification of children with respect to the outcome, wheezing or asthma, is likely to occur. There is no epidemiological gold standard for asthma [34] and differences between studies will arise merely because they use different definitions of asthma or wheezing. However, there has been some standardisation, based particularly on use of the American Thoracic Society, Division of Lung Disease questionnaire [93] which identifies 'persistent wheezing' as well as doctor-diagnosed asthma. Among studies which used some version of the standard

questions, there is consistency [37,44, 50,52,58], although not unanimity [11].

Could the positive association found in a number of studies be accounted for by confounding? This is a consideration wherever the measure of effect is modest. Important potential confounders that have been identified are socioeconomic status (SES), parental symptoms and active smoking in childhood.

SES is an indicator of a wide range of influences which affect health. Children of lower SES may be subject to other air pollutants, poorer housing quality and nutrition, and less access to decent health care than children who are well off. To the extent that these factors individually or collectively increase the risk of asthma, and in addition are more common among the children of smokers, they may produce an exaggerated relationship between passive smoking and asthma, i.e. confounding.

Most studies have found wheezing to be more common among children of lower SES or of less educated parents [8,36,41, 45,58,94], although this is not clearly the case of children who have been diagnosed asthmatic [8,12,54], suggesting a differential likelihood of diagnosis by SES. Passive smoking is also likely to be more common among children of lower SES, although in the United States this varies by ethnic background [95,96]. However, most of the positive studies reviewed have included some variable to denote social class difference, frequently parental education, without eliminating the effect of maternal smoking.

The simultaneous measurement of a number of variables such as family size [97], home dampness [46,53] and maternal care factors [98], might be needed to adjust fully for the range of social class-related influences [94].

The observation that parents who are themselves symptomatic report more respiratory symptoms in their children [8,9,10,11,58] has been interpreted as requiring adjustment for such parental symptoms as a potential confounder [2]. Such adjustment has led to some attenuation but not elimination of the association between parental smoking and asthma or wheezing [9,38,44,51,58]. However, this association between parental and child's symptoms may not be due to overreporting, but to the common direct response to tobacco smoke, to cross-infection in smoking households [96] or to hereditary tendencies in asthma [8,99]. In such cases, adjustment for parental symptoms may result in a degree of overadjustment [4].

Active smoking by the child is another potential confounder in studies of children over about seven years of age, as children of smoking parents are more likely to try smoking themselves. In the positive studies of older children which inquired about active smoking by the child, one [44] controlled for such smoking, another [58] found smoking to be rare among six- to nine-year-olds, while a third [49] found no daily smoking among a subgroup of sixth graders who were questioned. However, underreporting by older children of their smoking habits is probable and some degree of confounding may occur.

Conclusion

The association between maternal smoking and asthma and wheezing illness in children satisfies a number of the criteria for causality [2]. There is reasonable consistency among studies, an exposure-response relationship has been demonstrated and an appropriate temporal relationship established in prospective studies.

In addition, the association has biological plausibility although the mechanism remains to be defined, and there is not strong evidence that confounding accounts for the observed increase in risk.

From a public health perspective the impact of such a causal relationship is considerable. Assuming a relative risk of asthma due to maternal smoking of 1.5, after controlling for confounding, and a maternal smoking prevalence of 30% [95], an attributable proportion of 13% can be calculated [100]. This is the proportion of asthma and persistent

wheeze in childhood that could be prevented in the absence of maternal smoking. This should add further weight to public health, clinical and educational efforts to reduce the burden of illhealth imposed on young children by the tobacco smoking habit.

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PARENTAL SMOKING AND OTITIS MEDIA IN CHILDREN

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PARENTAL SMOKING AND OTITIS MEDIA

There are studies which claim to have found an association between exposure to ETS and the occurrence of a relatively common childhood ear condition called otitis media with effusion (OME). However, the reported data are inconsistent, and even contradictory, in nature. For example, while eight studies have reported a statistically significant association between parental smoking and middle ear problems in children,[1-8] ten studies have reported no statistically significant association.[9-17]

In regard to OME, an inflammation of the eustachian tube that can lead to the accumulation of fluid in the inner ear, a group of Dutch researchers has asserted that "there is little evidence that parental smoking has an effect on the risk for OME," although they noted that "the literature is not consistent."[11] Their own study indicated that while the occurrence of OME was not related to exposure to ETS in the home, variables relating to age, season, family size, sibling's history of OME, frequent swimming, and public day care attendance had a "significant effect." A Scottish study which did report an association between parental smoking and OME noted that the prevalence of parental smoking was higher in rented or crowded homes, and in homes affected by dampness or mould growth.[13] A 1993 study by Rasmussen, et al., while reporting that there was an association between day care attendance and otitis media, suggested that "no association was found between parents' smoking habits and the incidence of protracted SOM

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[secretory otitis media]."[17] Clearly, these reports suggest there is a need to evaluate additional factors in any study of the potential relationship between OME and parental smoking.

While a couple of studies in 1992 reported an association between parental smoking and otitis media[7-8], a 1991 study by Daigler et al. reported that they were "unable to confirm the association between [parental] smoking and otitis" that had been "reported by others."[14] Another group of authors reported that cigarette smoking is more common in households of lower socioeconomic status but that "it is unlikely to be a risk factor for otitis media with effusion, although it may have an association."[15] Similarly, a 1992 study by Rowe-Jones et al. failed to report a statistical association between parental smoking and otitis media with effusion requiring grommet insertion.[16]

Other researchers recently acknowledged that questionnaire reports of acute OME may be an inadequate method of determining the incidence of the condition in epidemiological studies.[18] Therefore, until a more accurate method of determining the incidence of OME is found, isolating parental smoking as a cause is seemingly unjustified.

Reports that parental smoking causes otitis media in children are contradicted by studies reporting no association between parental smoking and OME. The methods used in these studies

to estimate exposure to ETS and the incidence of OME are seemingly inaccurate. Thus, the role, if any, of parental smoking has yet to be determined.

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OTITIS MEDIA "GLUE EAR"

TWO PROPOSED MECHANISMS (HAVE NOT BEEN PROVEN)

1. ETS LEADS TO AN UPPER RESPIRATORY INFECTION WHICH SPREADS TO THE INNER EAR

2. TOBACCO SMOKE IRRITATES THE EUSTACHIAN TUBE OF THE INNER EAR, LEADING TO THE INFLAMMATION/INFECTION

PARENTAL SMOKING AND MIDDLE EAR DISEASE IN CHILDREN

STUDY	SIGNIFI-CANCE	SYMPTOMS OR ILLNESS (AGE IN YEARS/NUMBER OF SUBJECTS)
KRAEMER ET AL.	+	MIDDLE EAR EFFUSION (AGES NOT GIVEN/152)
MARCHISIO ET AL.	-	MIDDLE EAR EFFUSION (5 MONTHS-12 YEAR/172)
PUKANDER AND KARMA	-	MIDDLE EAR EFFUSION (7-29 MONTHS/753)
ROCKLEY	-	CHRONIC SEROUS OTITIS MEDIA (4-14/78)
VAN CAUWENBERGE AND KLUYSKENS	-	MIDDLE EAR EFFUSION (2.5-6/2,069)
BLACK	+	SEROUS OTITIS MEDIA (4-9/442)
IVERSEN ET AL.	+	MIDDLE EAR EFFUSION (<7/337)
PUKANDER ET AL.	+	ACUTE OTITIS MEDIA (2-3/471)
FLEMING ET AL.	-	OTITIS MEDIA (<5/575)
KALLAIL ET AL.	-	MIDDLE EAR 'PROBLEMS' (6-10 OR 11/238)
REED AND LUTZ	+	MIDDLE EAR EFFUSION (AGES NOT GIVEN/45)
ZIELHUIS ET AL.	-	MIDDLE EAR EFFUSION (3/<1,439)
HINTON	-	SURGERY FOR OTITIS MEDIA WITH EFFUSION (1-12/151)
STRACHAN ET AL.	+	MIDDLE EAR EFFUSION (6.5-7.5/736)
ROSS ET AL.	-	ACUTE OTITIS MEDIA (3-5/297)
STRACHAN	-	TYPE B TYMPANOGRAM (MIDDLE EAR EFFUSION); TYPE C TYMPANOGRAM (UNDER PRESSURE) (6.5-7.5/872)
STRACHAN ET AL.	-	'EAR TROUBLE' (6.5-7.5/770)
DAIGLER ET AL.	-	ACUTE OTITIS MEDIA (2-6/371)
BARR ET AL.	-	MIDDLE EAR EFFUSION AND OTITIS MEDIA (17 MONTHS-11 YRS/115)

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ROWE-JONES ET AL.	-	OTITIS MEDIA WITH EFFUSION (2-12 YRS/163)
ETZEL ET AL.	+	MIDDLE EAR EFFUSION (0-3 YRS/132)
MAW ET AL.	+	OUTCOME AFTER TREATMENT FOR OTITIS MEDIA (2-9 YRS/201)
RASMUSSEN	-	PROTRACTED SECRETORY OTITIS MEDIA (0-7 YRS/1306)
SUMMARY	8:15	

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OTITIS MEDIA: COTININE STUDIES

STRACHAN ET AL. 1989 RR = 1.14 (95% CI: 1.03-1.27)*

*THE ODDS RATIO IS FOR A DOUBLING OF THE COTININE CONCENTRATION FOUND IN THE SALIVA OF THE CHILD.

NOTE: THE AUTHORS OF THIS STUDY CONCLUDED THAT "ABOUT ONE THIRD OF THE CASES OF MIDDLE EAR EFFUSION IN THIS STUDY WERE STATISTICALLY ATTRIBUTABLE TO EXPOSURE TO TOBACCO SMOKE."

ETZEL ET AL. 1992 RR = 1.38 (95% CI: 1.21-1.56)*

*THE ODDS RATIO IS FOR CHILDREN WITH SERUM COTININE CONCENTRATIONS OF 2.5 NG/ML.

NOTE: THE AUTHORS OF THIS STUDY CONCLUDED THAT "8% OF THE CASES OF OTITIS MEDIA WITH EFFUSION IN THIS POPULATION AND 17.6% OF THE DAYS WITH OTITIS MEDIA WITH EFFUSION MAY BE ATTRIBUTABLE TO EXPOSURE TO TOBACCO SMOKE."

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Said, G., Zalokar, J., Lellouch, J., Patois, E. "Parental smoking related to adenoidectomy and tonsillectomy in children" <u>Journal of Epidemiology and Community Health</u> 32(2): 97-101, 1978.

The authors of this study investigated the histories of adenoidectomy and tonsillectony and parental smoking habits for 3920 school children aged 10 to 20 years. The two surgical procedures were considered to be indexes of repeated upper respiratory tract disease in early childhood. The authors reported that both procedures were significantly related to the amount of smoking by each parent in this study. The authors claim that the relationships remained after they controlled for age, sex, day nursery attendance, sibship size, and history of appendicectomy.

(2)
Journal of Epidemiology and Community Health, 1978, 32, 97-101

Parental smoking related to adenoidectomy and tonsillectomy in children

G. SAID
From Bagneux, Paris, France

J. ZALOKAR, J. LELLOUCH, AND E. PATOIS
From Unité de Recherches Statistiques, INSERM, Villejuif, France

SUMMARY Histories of adenoidectomy and tonsillectomy were ascertained, as well as smoking habits of both parents, using questionnaires answered by 3920 schoolchildren aged 10 to 20. [redacted]

Introduction

[redacted] 6 to 14 was related to smoking by [redacted] This relationship appeared to be indirect and cross-infection was an important element, as the prevalence was doubled among children whose parents had respiratory symptoms not associated with smoking. [redacted] Over the age of one year, the incidence was related only to parental respiratory symptoms.

[redacted] smoking habits of adults in their households, but not significantly so when similar respiratory symptoms in household adults were controlled. Harlap and Davies (1974) studied hospital admission rates during the first year of life of infants whose mothers' smoking habits were known. The babies of smoking mothers were more often admitted for bronchitis and pneumonia, but there was no significant difference in admission rates for upper respiratory tract infections. This negative result is in contrast with experimental findings that in animals placed in a smoke-filled atmosphere, a [redacted]

We present here the results of an investigation of the relationship between adenoidectomy and/or tonsillectomy in children, selected as an index of upper respiratory tract disease, and smoking by their parents.

Methods

Although the prevalence of upper respiratory tract disease is difficult to estimate directly, the child with repeated attacks is often, rightly or wrongly, subjected to adenoidectomy at about one year of age, and/or tonsillectomy at about five years of age. For this reason, we chose history of adenoidectomy and/or tonsillectomy (A or T) as an index of the prevalence of upper respiratory tract disease. Since these operations occur in early childhood, they precede any smoking by the child himself.

In 1975-76, students in nine secondary schools in Paris were given questionnaires to fill in by themselves in class. The questions covered sex; age; number of siblings; day nursery attendance before the age of three; smoking habits of mother (choices: non-smoker, 1 to 5, 6 to 10, 11 to 20, or more than 20 cigarettes a day) and father (choices: the same + pipe or cigars); and history of adenoidectomy, tonsillectomy, and appendicectomy. This last was

Table 1 *Percentages (total numbers) of children reporting adenoidectomy and/or tonsillectomy by amount of smoking by each parent, as reported by their children*

	FATHERS						
		No. of cigarettes a day					
	Non-smokers	*1–5*	*6–10*	*11–20*	*21+*	*Pipe and cigar only*	*ALL FATHERS*
MOTHERS							
Non-smokers	28 (1550)	37 (412)	39 (380)	48 (305)	54 (175)	31 (157)	35 (2979)
Cigarettes a day							
1–5	37 (110)	44 (123)	48 (87)	56 (62)	50 (42)	43 (58)	45 (482)
6–10	38 (74)	50 (34)	60 (83)	39 (38)	53 (19)	56 (18)	49 (266)
11+	51 (55)	47 (15)	58 (12)	67 (45)	48 (40)	58 (26)	55[2] (193)
ALL MOTHERS	30 (1789)	40 (584)	44 (562)	50 (450)	53 (276)	38[1] (259)	38 (3920)

[1] Test of significance of difference in % A or T by amount of smoking of fathers : $\chi^2 = 118{\cdot}0$, 5 DF, $P < {\cdot}001$
[2] Test of significance of difference in % A or T by amount of smoking of mothers : $\chi^2 = 63{\cdot}0$, 3 DF, $P < {\cdot}001$

intended as a control question. The children were not informed of the purpose of the questionnaire.

Less than 1% of the questionnaires lacked information on parents' smoking habits or on history of operations and these were rejected. The questionnaires of 3920 students (35·9% boys and 64·1% girls) aged 10 to 20 (except for 35 under the age of 10) were finally analysed. Information on number of siblings or sex was missing on 52 questionnaires (1·3%).

Very few children (56) reported that their mothers smoked more than 20 cigarettes a day, so they were grouped with those reporting maternal smoking of 11 to 20 cigarettes a day. Children whose fathers were reported to smoke both cigarettes and a pipe or cigars were grouped by paternal cigarette consumption, leaving a residual category of children whose fathers smoked a pipe or cigars only. The results were analysed using the x^2 test with Yates' correction where appropriate.

Results

Table 1 shows the percentage of children reporting A or T, or both, grouped by the smoking habits of each parent. In the lower section of the Table it can be seen that the percentage of A or T increased very markedly with the quantity of cigarettes smoked by the mother, and very significantly also with the number smoked by the father. There is an intermediate value for the group whose fathers smoked a pipe or cigars only.

Table 2 *Percentages (total numbers) of children reporting adenoidectomy and/or tonsillectomy by age and sex*

Age	*Boys*	*Girls*	*Total by age*
< 15	40 (633)	36 (1308)	37 (1941)
15+	44 (766)	35 (1196)	38 (1962)
Total by sex	42 (1399)	36 (2504)	

Difference between boys and girls significant at 0·1% level.
Difference between ages not significant overall or for either sex.

If the smoking habits of both parents are considered simultaneously, the frequency of A or T was higher when both parents smoked than when only one did, except when one parent was a heavy smoker. Thus, while 28% of the children with two non-smoking parents reported a history of A or T, calculations summarising Table 1 show that 42% of the children with one smoking parent, and 51% of the children with two smoking parents, reported such a history.

Boys reported A or T more frequently than girls (Table 2). Age differences were not significant. Children who had attended a day nursery also reported A or T more frequently than non-attenders (47% compared with 37%). The percentage of children reporting A or T decreased regularly overall from 47% of only children to 29% of those with three or more siblings (Table 3), but considered separately by sex and number of smoking parents (both these variables interact with family size),

there was no general drop in percentage A or T until family size reached two or more siblings. Nevertheless, the strong relationship between parental smoking and history of A or T was found in both sexes and in all sibship sizes, irrespective of day nursery attendance, and in eight of the nine schools, drawing pupils from a variety of socio-economic strata. The association was not significant in the ninth school, where only 36 children took part.

A significant association was found between amount of maternal (but not paternal) smoking and percentage of appendicectomies (Table 4, totals). This was mainly due to the increased frequency of appendicectomy in children with a history of A or T (25%) compared to those without such a history (16%). But a weak association did remain between appendicectomies and amount of maternal smoking among children without a history of A or T. Appendicectomies were reported significantly more often in girls (20%) than boys (18%) but the slightly higher proportion of older children reporting this operation was only marginally significant and there was no relationship to number of siblings.

Discussion

Our study confirms the finding of an association between parental smoking and the prevalence of persistent upper respiratory tract disease in their children as indicated by adenoidectomy or tonsillectomy. However, some points need further elucidation.

First, how valid are reports by those aged 10 to 20 of operations that may have occurred in the first few years of life? As a rule, children are aware of their past operations, partly because of the importance attached to these by their parents, and partly because of the many medical forms they will have filled in at school. The overall proportion reporting A or T (38%) seems to correspond to medical practice in the early 1960s. We note that the reporting of day nursery attendance, another event occurring before three years of age, followed the expected demographic pattern: it was most often reported among only children, and least often among those with three or more siblings.

The proportion (19%) reporting appendicectomy may appear surprisingly high in comparison with that

Table 3 *Percentages (total numbers) of children reporting adenoidectomy and/or tonsillectomy by sex, number of siblings, and smoking habits of parents as reported by their children*

No. of siblings	Boys: No. of smoking parents 0	1	2	Girls: No. of smoking parents 0	1	2	Total	Test of significance* Boys	Girls
0	29 (69)	55 (96)	75 (36)	34 (97)	51 (120)	57 (46)	47 (464)	$\chi^2 = 22{\cdot}2$, $P < {\cdot}001$	$\chi^2 = 8{\cdot}8$, $P < {\cdot}02$
1	38 (180)	56 (151)	52 (93)	32 (280)	44 (248)	56 (135)	44 (1087)	$\chi^2 = 12{\cdot}6$, $P < {\cdot}005$	$\chi^2 = 21{\cdot}9$, $P < {\cdot}001$
2	34 (144)	44 (145)	55 (64)	27 (237)	39 (284)	50 (103)	38 (977)	$\chi^2 = 8{\cdot}4$, $P < {\cdot}02$	$\chi^2 = 17{\cdot}8$, $P < {\cdot}001$
3+	25 (162)	33 (180)	53 (62)	18 (353)	33 (428)	37 (155)	29 (1340)	$\chi^2 = 16{\cdot}4$, $P < {\cdot}001$	$\chi^2 = 31{\cdot}2$, $P < {\cdot}001$
Total	32 (555)	46 (572)	56 (255)	26 (967)	39 (1080)	48 (439)		$\chi^2 = 47{\cdot}2$, $P < {\cdot}001$	$\chi^2 = 76{\cdot}0$, $P < {\cdot}001$

*Test of significance of difference in % A or T by number of smoking parents : χ^2 with 2 DF

Table 4 *Percentages (total numbers) of children reporting appendicectomy by amount of smoking of each parent and by whether or not they also reported A or T*

A or T	Mothers: Non-smoker	No. of cigarettes a day: 1–5	6–10	11+	Test of significance
No	15 (1951)	17 (264)	21 (136)	24 (87)	$\chi^2 = 8{\cdot}7$, $P < {\cdot}05$
Yes	24 (1028)	23 (218)	25 (130)	36 (106)	$\chi^2 = 7{\cdot}4$, $P < {\cdot}10$
Total	18 (2979)	20 (482)	23 (266)	31 (193)	$\chi^2 = 20{\cdot}5$ DF = 3, $P < {\cdot}001$

A or T	Fathers: Non-smoker	No. of cigarettes a day: 1–5	6–10	11–20	21+	Pipe or cigars only	Test of significance
No	17 (1259)	13 (352)	15 (313)	18 (223)	20 (131)	12 (160)	$\chi^2 = 7{\cdot}2$, $P > {\cdot}20$
Yes	23 (530)	24 (232)	28 (249)	28 (227)	26 (145)	22 (99)	$\chi^2 = 3{\cdot}7$, $P > {\cdot}50$
Total	19 (1789)	17 (584)	20 (562)	23 (450)	23 (276)	16 (259)	$\chi^2 = 11{\cdot}0$ DF = 5, $P < {\cdot}06$

in English-speaking countries. In French medical practice, appendicectomy can be considered as an index of the incidence of acute abdominal conditions rather than appendicitis. In fact, since all doubtful cases are resolved in favour of appendicectomy, a perforated appendix is rarely seen here. The fact that more girls than boys reported appendicectomy accords with the preponderance of girls among older children with recurrent abdominal pain (Dodge, 1976).

The strong association between history of A or T and appendicectomy may have been due to several factors. There is, firstly, the possibility that some children answered positively (or negatively) to all three questions about operations; but the fact that appendicectomies showed a different demographic pattern than A or T tends to increase confidence in the validity of the self-reporting of operations by these schoolchildren. Then there is the positive association between social class and number of elective operations that has been found in the United States and Europe (Roos *et al.*, 1977; Wingerd and Sponzilli, 1977). Furthermore, independent of social class, there may be 'operation prone' children, at the mercy of their parents' or family doctors' predilections. On the other hand, some proportion of children presenting with acute abdominal conditions do in fact have upper respiratory infections (British Medical Journal, 1976; Dodge, 1976; Jones, 1976).

Secondly, how valid is information about parental smoking provided by those aged 10 to 20, and how are present smoking habits related to those of perhaps 15 years ago at the time of the A or T? The proportions of children reporting both parents non-smokers (40%), one parent smoking (42%), and both parents smoking (18%) were consistently the same for both sexes and for all age groups. Compared with a study of Paris policemen aged 46 to 52 (Zalokar *et al.*, 1974), less smoking by fathers was reported, but compared with a study of pregnant women in Paris (Schwartz *et al.*, 1972), more smoking by mothers was reported. Smoking by men in France is negatively related to social class and the proportion of men who stop smoking increases after the age of 45. By contrast, smoking by pregnant women is positively related to social class. Judging from the present study, maternal smoking may increase with age. It must be noted, however, that changes in parental smoking habits after the epoch of A or T would lead to an underestimation of the relationship of these variables.

More seriously, it is possible that the children who reported A or T or appendicectomy were more inclined to over-report parental smoking in spite of not knowing the purpose of the questionnaire. (Bias can also occur in the opposite direction when parents are asked about their own smoking habits in conjunction with their children's symptoms). This was the reason for our question about appendicectomy; we thought *a priori* that it would not be associated with parental smoking.

However, the weaker association between maternal [redacted] among children not reporting appendicectomy. The most likely explanation for the association of appendicectomy with maternal smoking is that both increase with the rising socio-economic status of the family. Also, since appendicectomy is generally performed at a later age than A or T, it may be more closely related to present maternal smoking habits.

Even so, social class cannot be considered [redacted]

Reprints from J. Zalokar, U. 169, Institut National de la Santé et de la Recherche Médicale, 16 bis, Avenue Paul Vaillant-Couturier, 94800 Villejuif, France.

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Vinther, B., Elbrond, O., Pedersen, C.B. "Otitis Media In Childhood, Socio-Medical Aspects With Special Reference To Day-Care And Housing Conditions" Acta Otolaryngol 386(Supplement): 121-123, 1982.

This study was designed to determine the influence of day-care attendance and housing condition on the frequency of otitis media in childhood. Six hundred and eighty-one children, aged 3 to 4 years, were studied by taking somatic and social history, otological examination and tympanometry. The investigators found that earlier otitis media was 25% higher among children cared for outside home than among those cared for at home. Among the children attending day-care, there was also a statistically significant higher number of flat tympanometric curves and adenoidectomies. There were also statistically significant more children living in flats who had otitis media than there were children from houses. The children living in flats had a significantly higher number of adeniodectomies, but there was no difference between the children living in flats or homes in the number of flat tympanometric curves. The analysis showed that there were no effects of parental smoking or social status on the frequency of otitis media, adenotomy or tympanometric findings.

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H. PUHAKKA J. SUONPÄÄ

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OTITIS MEDIA IN CHILDHOOD. SOCIO-MEDICAL ASPECTS WITH SPECIAL REFERENCE TO DAY-CARE AND HOUSING CONDITIONS

Bent Vinther, Ole Elbrønd & Chr. Brahe Pedersen

From the Department of Otorhinolaryngology, University Hospital of Aarhus, Denmark

Abstract. In order to elucidate the influence of day-care and housing condition on the frequency of otitis media, 681 children, 3—4 years old, were investigated by taking somatic and social history, otological examination and tympanometry.

At the time of investigation 76 % of the children were cared for outside their home and one third was taken care of outside their home at the age of 3 months.

Among the children cared for outside home the history of earlier otitis media was 25 % higher than among those at home; at the same time there were statistically significant more flat tympanometric curves and adenoidectomies.

Regarding housing condition there were statistically significant more children with acute otitis media in flats than in houses, especially in newer concrete flats built after 1960, and there were significantly more adenoidectomies in those flats.

Tympanometry revealed no difference in respect to housing condition.

With a view to the elucidation of the incidence of otitis media in childhood and the relation of this problem to social factors, 681 children all 3—4 years old from the Aarhus district were studied.

METHOD

The children studied were divided into four groups as shown in Table I. Of the series of 681 children, 336 were girls and 345 boys. The clinical study consisted in the taking of a thorough somatic and social history, including information on day-care and housing conditions and an otological examination including tympanometry.

Concerning day-care condition the question asked focused on the time when the children first began to attend day-care nurseries, kindergarten or if they were cared for by a baby minder in a family day-care home. Concerning housing condition it was asked for if they lived in a flat or house, type of building material, number of rooms and construction year.

Table I. *The number of children studied divided into four groups*

	No.
Randomly selected	287
Houses	119
Poor housing conditions	133
Concrete apartments	142
Total	681

RESULTS

The frequency of children cared for outside their homes related to age is shown in Fig. 1. After 3 months one third is cared for outside home and at the age of 4 years 76 % is cared for outside home.

Of the children cared for outside home 60 % started primarily at a baby minder while 40 % primarily started in day nursery or kindergarten.

Among the children cared for outside home the history of earlier otitis media was 25 % higher than among those at home, respectively 40 % and 32 % (Fig. 2). Children who attended day-care outside home before the age

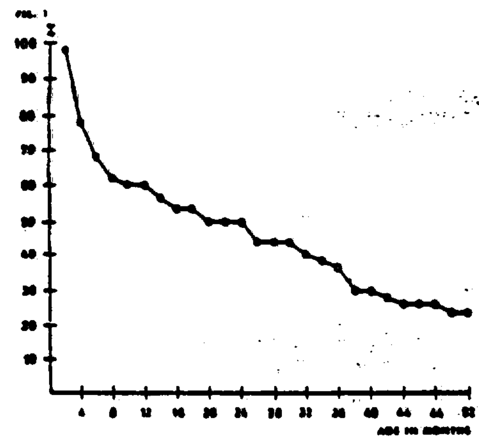

Fig. 1. Survival curve demonstrating age for first day-care outside home.

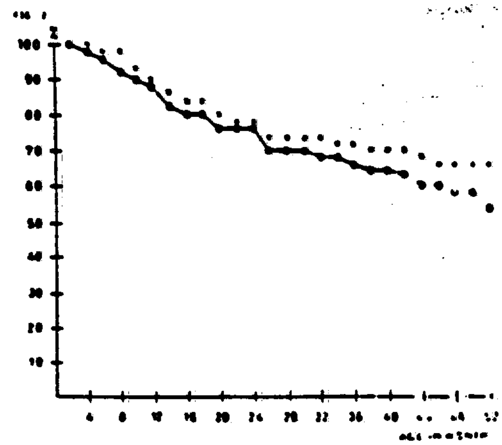

Fig. 2. Survival curve for first acute otitis media related to: day-care at home (x — x) and day-care outside home (o — o).

of 6 months had statistically significant more otitis media than children at home ($p < 0.05$). There were more boys than girls with a history of earlier otitis media and there were statistically significant ($p < 0.05$) more boys with ear discharge.

Children with earlier otitis media had an average of 2.7 attacks each and 97 % of these were treated with penicillin.

Tympanometry revealed that there were statistically significant ($p < 0.05$) more children with flat tympanometric curves (Type B) among children attending day-care than among children at home (Table II).

Table II. *Tympanometric findings (no. of ears) related to type of day-care*

	Outside home		At home	
	N	%	N	%
Normal pressure (Type A curves)	571	59	223	65
Flat curves (Type B curves)	148	15	26	8
Negative pressure (Type C curves)	252	26	93	29

Adenotomy is most commonly performed in patients with chronic infection of the nasopharynx. 14 % of the children attending day-care outside home had undergone adenotomy versus only 7 % among the home-cared children (difference statistically significant $p < 0.01$).

There was statistically significant ($p < 0.01$) sex difference in the children who underwent adenotomy since there were only 30 girls versus 55 boys.

According to housing conditions there was statistically significant more children with otitis media living in flats than in houses, and especially was there a higher otitis media frequency in flats built after 1960 (Table III). The study revealed the same tendency fo adenotomy (Table IV).

The tympanometric findings showed no difference in the occurence of secretory otitis media in the four different housing conditions.

Table III. *Number of 3—4 year old childre with previous otitis media classified in house flats built before and after 1960*

	Before 1960		After 196C	
	N	%	N	
Houses	21/62	34	78/237	.3
Flats	72/190	38	87/187	.7

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Table IV. *Number of 3—4 year old children with previous adenoidectomy classified in houses/flats built before and after 1960*

	Before 1960		After 1960	
	N	%	N	%
Houses	3/59	5	16/237	7
Flats	25/189	13	42/185	23

Looking at the housing condition and type of day-care at the same time (Table V) you find — as expected — that the best constellation with respect to low incidense of otitis media is care at home and living in an older house, and the worst is day-care outside home and living in a newly built flat.

The analysis shows that the social status and the smoking habits of the parents do not have any influency on the frequency of otitis media, adenotomy or the tympanometric findings.

Table V. *Number of 3—4 year old children with previous otitis media classified in houses/flats and type of day-care*

	Houses		Flats	
	N	%	N	%
At home	23/88	26	32/84	38
Outside home	76/211	36	127/293	43

DISCUSSION

Among the factors which have influence on the frequency of otitis media we have pointed out type of day-care and housing condition.

The reason for a greater amount of morbidity for children cared for outside home is presumably a consequence of higher frequency of upper respiratory infections in day-care centers (Strangert, 1976).

The change in life style, where now more than three third of all children are cared for outside home, is probably the reason why otitis media occurs earlier in life than before (Platt, 1957).

Our statistical analysis has shown that the increased morbidity in newly built flats can not be explained from type of day-care, social status, smoking habits or sex. The four types of housing conditions are also fully comparable to the number of working hours the mother is spending outside home. It must therefore be assumed that the four groups of children are comparable and that the higher frequency of otitis media and adenotomy among children may be due to a factor inherent in newly built flats.

Of the flats built after 1960, 92 % were constructed of concrete, versus only 9 % before 1960. The higher frequency of otitis media and adenotomy in younger children might be due to a change in indoor climate caused by increased insulation and/or change of building materials — our investigation has not clarified this question (WHO-Report, 1979).

The above observations on the importance of day-care and housing conditions on morbidity are so interesting that they should encourage further research on the influence of indoor climate on health conditions — not least in children.

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Bent Vinther, M.D.
Department of Otorhinolaryngology
University Hospital of Aarhus
DK-8000 Aarhus C
Denmark

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Kraemer, M.J., Richardson, M.A., Weiss, N.S., Furukawa, C.T., Shapiro, G.G., Pierson, W.E., Bierman, C.W. "Risk Factors for Persistent Middle-Ear Effusions: Otitis Media, Catarrh, Cigarette Smoke Exposure, and Atopy" Journal of the American Medical Association 249(8): 1022-1025, 1983.

SUMMARY: To ascertain risk factors for persistent middle-ear effusions (PMEE), we interviewed the parents of two groups of children. The first consisted of 76 children with PMEE who were admitted to the hospital for tympanostromytube insertion. The second, a control group, consisted of 76 children admitted for other types of surgery, who were matched for age, sex, season, and surgical ward. Nearly all (97%) of the children admitted for insertion of tympanostomy tubes had one or more episodes of suppurative otitis media. Only 59% of the control children had previous ear infections. Frequent ear infections sharply increased the risk for persistent effusions. Catarrh, household cigarette smoke exposure, and atopy also occurred more frequently in children with PMEE. The risk for middle-ear effusions was greatest when these three factors were all present. The avoidance of daily exposure to domestic tobacco smoke and, if atopic, of specific allergens should be included in the medical treatment of children with PMEE.

Original Contributions

Risk Factors for Persistent Middle-Ear Effusions

Otitis Media, Catarrh, Cigarette Smoke Exposure, and Atopy

Michael J. Kraemer, MD; Mark A. Richardson, MD; Noel S. Weiss, MD, DrPH; Clifton T. Furukawa, MD; Gail G. Shapiro, MD; William E. Pierson, MD; C. Warren Bierman, MD

• To ascertain risk factors for persistent middle-ear effusions (PMEE), we interviewed the parents of two groups of children. The first consisted of 76 children with PMEE who were admitted to the hospital for tympanostomy-tube insertion. The second, a control group, consisted of 76 children admitted for other types of surgery, who were matched for age, sex, season, and surgical ward. Nearly all (97%) of the children admitted for insertion of tympanostomy tubes had one or more episodes of suppurative otitis media. Only 59% of the control children had previous ear infections. [redacted]

(*JAMA* 1983;249:1022-1025)

MIDDLE-EAR effusions are common in children, particularly after a suppurative middle-ear infection.[1,2] Most effusions resolve after several weeks, but some persist relentlessly,[3,4] causing hearing loss[5] and associated language, behavioral, and learning deficits.[6-10] Each year in the United States, an estimated 1 million operations take place in which tympanostomy tubes are inserted for persistent middle-ear effusions (PMEE).[11]

Several factors may affect the frequency of middle-ear disease: age,[1,11] sex,[12,13] season,[4] socioeconomic class,[13] exposure to other children,[3,14] catarrh,[3,4,5] positional feeding styles,[3,15] atopy,[16,17] and a family history of ear disease.[1] In this study, we examined the association of these *factors* with the persistence of middle-ear effusions.

METHODS

The Research Committee and the Human Rights Committee at the Children's Orthopedic Hospital and Medical Center, Seattle, reviewed and approved these procedures. All parents gave informed consent before interview.

Case Selection

From June through October 1981, two general pediatric otolaryngologists performed 96 bilateral myringotomy and tympanostomy-tube insertions (BMT) for PMEE. Children were treated surgically if they had bilateral effusions (with pneumatic otomicroscopy and tympanometry) that did not resolve after eight or more weeks of medical therapy, and which produced a hearing loss of 25 dB or greater. These children were admitted to a short-stay ward at the Children's Orthopedic Hospital and Medical Center for surgery. Their parents were asked to participate in an interview about risk factors for ear disease. We interviewed 76 parents of the 96 patients with PMEE. Of the 96 patients' families, two were excluded because they did not speak English, and 18 could not be reached.

Control Selection

Twelve physicians (four general surgeons, one urologist, one ophthalmologist, two dental surgeons, and four cardiologists) allowed us to contact parents of their patients admitted during the same period to the same short-stay surgery ward. From this group of 202 children, control subjects were matched to PMEE cases by age (± 1 year), sex, and month of surgery. Ninety-five patients were matched initially, but 14 could not be contacted. Five interviews were excluded because of current middle-ear effusions or past ear surgery.

Clinical Characteristics of Cases and Control Subjects

Twenty-one patients with PMEE (27.6%) had previous bilateral tympanostomy-tube insertions (range, one to nine). Two patients with PMEE had Down's syndrome and two had cerebral palsy. In

From the Divisions of Otolaryngology (Dr Richardson) and Allergy (Drs Kraemer, Furukawa, Shapiro, Pierson, and Bierman), Children's Orthopedic Hospital and Medical Center, and the Departments of Otolaryngology, Pediatrics, and the School of Public Health (Dr Weiss), University of Washington School of Medicine, Seattle.

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the 76 control children, the reasons for admission were inguinal hernia repair (30), cardiac catheterization (17), biopsy or foreign-body removal (eight), umbilical, epigastric, or diaphragmatic hernia repair (six), orchiopexy (six), hydrocele repair (three), dental caries debridement (three), cystoscopy (one), esotropia repair (one), and proctoscopy (one). Down's syndrome occurred in only one control child who had cyanotic congenital heart disease. No other medical condition occurred more than once in either group.

Interview

Parents were interviewed within eight weeks of the scheduled surgery for the following information: (1) racial background, (2) family size, (3) health insurance status, (4) infant care and feeding practices, (5) household exposure to cigarette smoke, (6) frequency of suppurative otitis media (symptomatic ear infection treated with antibiotics), (7) frequency of catarrh (audible nasal breathing with rhinorrhea), (8) atopy (defined as one or more of the following disorders during the preceding 12 months: seasonal rhinitis [spring or summer sneezing, nasal itching, rhinorrhea, and nasal congestion]; asthma [recurrent wheezing, which improved with use of bronchodilators]; eczema [recurrent pruritic dermatitis, which improved with topical steroid therapy]), (9) family history of atopy, and (10) family history of significant middle-ear disease (six or more episodes of suppurative otitis media, or previous insertions of tympanostomy tubes).

Analysis

The likelihood of PMEE developing with a certain exposure was expressed as the relative risk and estimated using the Mantel-Haenszel method, standardizing for age (younger than 2 years, 2 years or older) and sex.[a] Ninety-five percent confidence intervals for each relative risk estimate were derived using the method of Miettinen.[a] For some factors, the relative risk changed with increasing exposure. We used an extension of the Mantel-Haenszel method[a] to test for a linear trend of changing relative risk.

RESULTS

Table 1 shows the frequency and relative risk for each of the interview variables. Patients and control subjects were similar in all socioeconomic and demographic categories. There were no significant differences in birth weight, early feeding patterns, the use of nighttime bottles, or daily exposure to other children. Exposure to two or more household cigarette smokers increased the risk for PMEE

Table 1.—Relative Risk of Persistent Middle-Ear Effusions (PMEE) According to Interview Variables

Characteristic	No. (%) of PMEE Cases (N=76)	No. (%) of Surgical Control Subjects (N=76)	Relative Risk*	95% Confidence Interval†
Demographic‡				
Sex				
M	45(59.2)	45(59.2)	...	...
F	31(40.8)	31(40.8)	...	...
Race				
White	65(85.5)	65(85.5)	1.0	...
Nonwhite	11(14.5)	11(14.5)	1.0	...
Household adults				
≥2	64(84.2)	63(82.9)	1.0	...
1	12(15.8)	13(17.1)	0.9	0.4-2.2
Siblings				
0	24(31.6)	17(22.4)	1.0	...
≥1	52(68.4)	59(77.6)	0.6	0.3-1.3
Health insurance				
Private	51(67.1)	56(73.7)	1.0	...
Nonprivate	25(32.9)	20(26.3)	1.4	0.6-2.6
Infant care‡				
Birth weight				
≥2,500	71(93.4)	72(94.7)	1.0	...
<2,500	5(6.6)	4(5.3)	1.3	0.3-5.0
First 6 mo				
Breast-fed only	23(30.3)	21(27.6)	1.0	...
Formula-fed only	33(43.4)	28(36.8)	1.1	0.5-2.7
Nighttime bottles (first 12 mo)				
Never used	47(61.8)	52(68.4)	1.0	...
≥5 nights per week	23(30.3)	21(27.7)	1.2	0.6-2.4
Daily exposure to other small children§				
None	37(48.7)	36(47.4)	1.0	...
At home only	14(18.4)	10(13.2)	1.4	0.5-3.6
At home and away	25(32.9)	30(39.4)	0.8	0.4-1.5
Irritant exposure				
Household cigarette smokers§				
0	38(50.0)	45(59.2)	1.0	...
1	19(25.0)	23(30.3)	1.0	0.5-2.1
≥2	19(25.0)	8(10.5)	2.8	1.1-7.0
Household cigarette use,§ packs per day				
None	38(50.0)	45(59.2)	1.0	...
0.1-0.9	11(14.5)	7(9.2)	1.9	0.7-5.3
1.0-1.9	13(17.1)	14(18.4)	1.1	0.5-2.6
2.0-2.9	7(9.2)	8(10.5)	1.0	0.3-3.1
≥3.0	7(9.2)	2(2.6)	4.1	0.9-19.2
Otitis media				
Suppurative otitis media,‖ episodes				
None	2(2.6)	31(40.8)	1.0	...
1-2	10(13.2)	23(30.3)	6.6	1.5-31.3
3-6	12(15.8)	19(25.0)	9.1	2.3-36.5
>6	52(68.4)	3(3.9)	168.7	40.4-687
Age at first otitis, mo				
≥6	37(48.7)	56(73.7)	1.0	...
<6	39(51.3)	20(26.3)	3.0	1.2-7.4
Family history of middle-ear disease				
Absent	42(55.3)	53(69.7)	1.0	...
Present	34(44.7)	23(30.3)	1.9	0.9-3.6
Nasal congestion (see text for definition)				
Frequency of symptoms,‖ days monthly				
None	31(40.8)	57(75.0)	1.0	...
<6	10(13.2)	6(7.9)	3.0	1.0-9.5
6-15	15(19.7)	6(7.9)	4.6	1.7-12.8
>15	20(26.3)	7(9.2)	5.3	2.0-12.5
Atopic disease (see text for definition)				
Frequency of atopic symptoms,§ days monthly				
None	54(71.0)	65(85.5)	1.0	...
1-15	7(9.2)	6(7.9)	1.4	0.4-4.5
>15	15(19.8)	5(6.6)	3.7	1.3-10.6

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Table 1.—Relative Risk of Persistent Middle-Ear Effusions (PMEE) According to Interview Variables (cont)

Characteristic	No. (%) of PMEE Cases (N=76)	No. (%) of Surgical Control Subjects (N=76)	Relative Risk*	95% Confidence Interval†
Atopic disease (cont)				
Family history of atopic diseases				
Absent	35(46.0)	36(47.4)	1.0	...
Present	41(54.0)	40(52.6)	1.1	0.6-2.0

*Standardized for age and sex by the method of Mantel and Haenszel.
†Approximate limits, calculated by the method of Miettinen.
‡Mean age ± SD was 3.52 ± 2.7 years for the PMEE cases and 3.37 ± 2.8 years for control subjects. Mean birth weight ± SD was 3,349 ± 591 g for PMEE cases and 3,335 ± 550 g for control subjects.
§Test for linear trend, comparing strata of increasing exposure (P=.046).
‖Test for linear trend (P<.001).
¶Test for linear trend (P<.05).

Table 2.—Combined Effects of Risk Factors for Persistent Middle-Ear Effusions (PMEE)

Attributes	No. (%) of PMEE Cases (N=76)	No. (%) of Surgical Control Subjects (N=76)	Relative Risk*†	95% Confidence Interval‡
None	16(21.0)	31(40.8)	1.0	...
Only 1 factor	28(36.8)	33(43.4)	1.6	0.7-3.6
Congestion (>1 day a month)	14(18.4)	7(9.2)	3.9	1.3-11.3
Smoking (>0.5 packs per day)	13(17.1)	22(28.9)	1.1	0.5-2.6
Atopy (>1 day a month)	1(1.3)	4(5.3)	0.5	0.05-4.6
2 factors combined	19(25.0)	8(10.5)	4.6	1.7-12.6
Smoking and congestion	11(14.5)	5(6.6)	4.3	1.3-13.9
Smoking and atopy	1(1.3)	0(0.0)	...	...
Congestion and atopy	7(9.2)	3(3.9)	4.5	1.1-18.7
All 3 combined	13(17.2)	4(5.3)	8.3	1.9-21.1

*Standardized for age and sex by the method of Mantel and Haenszel.
†Test for linear trend comparing none, one, two, and three factors (P<.001).
‡Approximate limits, calculated by the method of Miettinen.

nearly threefold. With household exposure to smoke from more than three packs of cigarettes per day, the risk increased fourfold.

Nearly all of the patients with PMEE had one or more previous episodes of suppurative otitis media. A significant trend of increasing relative risk occurred with increasing frequency of otitis media. When the first episode of otitis media occurred at younger than 6 months of age, there was an apparent threefold risk for PMEE. However, if the age at the first episode of otitis was standardized for the total number of episodes, the relative risk was only 1.6 (95% confidence interval, 0.6 to 4.5). Thus, early otitis media may increase the risk for more frequent episodes of suppurative otitis, but of itself does not significantly increase the risk for PMEE. A family history of ear disease increased the risk less than twofold, but despite this modest elevation, families with three or more affected members occurred only in the PMEE group.

Nasal congestion occurred more often, and was more persistent, in children with PMEE. With more persistent catarrh the risk increased from threefold to fivefold. Atopic diseases occurred twice as often in children with PMEE. In those who required repeated tympanostomy-tube insertion, ten (48%) of 21 had atopic disease. The risk for PMEE increased nearly fourfold in children with persistent atopic symptoms. A family history of atopic disease did not increase the risk for PMEE.

Table 2 shows the combined effects of nasal congestion, cigarette smoke exposure, and atopy. Nasal congestion alone elevated the risk nearly fourfold. When cigarette smoke exposure or atopy was added to nasal congestion, the risk increased. Children with all three factors were more than six times as likely to manifest PMEE.

COMMENT

Suppurative otitis media, catarrh, household cigarette smoke exposure, and atopy are important risk factors for the development of PMEE. The risk increases with more long-term exposure. Several clinical and laboratory studies would substantiate the importance of these factors. Recurrent infections can damage ciliary function and cause metaplastic changes in middle-ear mucous glands. The altered mucosa secretes a thick, gluelike fluid, which is more likely to persist for long periods. Catarrh, which occurs more commonly in children with abnormal middle-ear pressures, may reflect repeated nasal infections, nasal irritant reactions, or nasal allergy. Each of these conditions could cause mucosal edema, hypersecretion, and abnormal ciliary function, which then results in obstruction or "dysfunction" of the eustachian tubes. Passive childhood cigarette smoke exposure increases the frequency of nonallergic respiratory symptoms [illegible] and may aggravate respiratory allergies. In heavily exposed children, catarrh from infection or allergies could become more persistent. In children with atopic disease, allergic rhinitis is the likely cause of their increased risk of middle-ear effusions. Recent studies in patients with allergies have shown that nasal challenges with specific antigens can produce sustained abnormalities of eustachian tube function.

Recurrent otitis media, nasal catarrh, cigarette smoke exposure, and nasal allergies chronically inflame the nasal and middle-ear cavities, causing persistent eustachian tube dysfunction. Middle-ear effusions will clear less readily in heavily exposed children, which may eventually necessitate surgical drainage and insertion of tympanostomy tubes. For these children, a medical treatment plan should include the elimination of tobacco smoke from the domestic environment and, if atopic disease is present, the control of specific environmental allergens.

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James Donaldson, MD, Barb Anderson, RN, and Donnie Lavery provided help in contacting patients. The physicians, surgeons, and support staff of the Children's Orthopedic Hospital and Medical Center, Seattle, provided assistance in contacting control subjects. Nancy Kraemer assisted in preparation of the manuscript.

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conditions of these patients were all maintained with placebo capsules for at least five to seven days during the withdrawal phase. While clear symptoms of withdrawal were observed, no severe reactions (eg, seizures or psychotic reactions) occurred. In keeping with our findings, few instances of severe withdrawal reactions associated with termination of *clinically accepted* doses of benzodiazepines have been reported in the literature. In the case reports cited by Drs Bargmann and Wolfe, the observations were made in uncontrolled conditions in which other factors may have been responsible for the reactions noted. In light of the widespread use of the benzodiazepine compounds, it is striking that so few instances of extreme withdrawal symptoms have been reported. However, more research, conducted under appropriately controlled conditions, is needed to evaluate this issue.

Drs Bargmann and Wolfe also raise questions about the efficacy of benzodiazepines in long-term use. Our recent report addresses this issue in only a preliminary manner. We are currently analyzing, for future publication, data from our study that support more directly the efficacy of long-term diazepam therapy.

Karl Rickels, MD
University of Pennsylvania
Philadelphia

Risk Factors for Persistent Middle-Ear Effusions

To the Editor.—Kraemer et al[1] compared children with persistent middle-ear effusion (PMEE) admitted to a hospital for tympanostomy tube insertion with children admitted for other types of surgery and matched to patients with PMEE by age, sex, season, and surgical ward. Parents were interviewed about children's household exposure to cigarette smoke, frequency of nasal congestion, and frequency of defined atopic symptoms. The ratios of the proportions of children with PMEE to the proportions of children without PMEE in whom these factors were present were expressed as relative risks.

When relative risks were calculated individually for nasal congestion, cigarette smoke exposure (as measured by whether household residents reportedly smoked more than 0.5 packs per day), and atopy, nasal congestion was significantly different in children with and without PMEE, but cigarette smoke exposure and atopy were not. When risks were calculated for the three factors in pairs, exposure to cigarette smoke plus congestion and congestion plus atopy were significantly more frequently present in children with PMEE than in those without PMEE. Cigarette smoke exposure plus atopy could not be tested because of inadequate numbers of subjects. When all three factors were combined, the combination was significantly more frequent in children with PMEE than in those without PMEE.

Data derivable from the article's Table 2 show that when the influence of nasal congestion is controlled in the analysis of the influence of exposure to smoking on PMEE, the children exposed to smoking and those not exposed differed little in the proportion who had PMEE (Table).

Similar calculations show that, within the congestion and no-congestion groups, the proportions of atopic and nonatopic children who had PMEE were similar—74% and 68%, respectively, in those with congestion and 33% and 35%, respectively, in those without congestion.

Using other cutoff points and other measures of cigarette smoke exposure (Table 1), the authors found, in the small numbers of subjects with the highest levels of exposure, differences in relative risk between subjects with and without PMEE that were of borderline statistical significance, but they did not find a linear trend of increasing risk with increasing exposure.

The authors interpreted the analyses they reported as indicating that nasal congestion, cigarette smoke exposure, and atopy were all "important risk factors." We believe instead that the apparent associations between cigarette smoke exposure and PMEE, and between atopy and PMEE are probably artifactual and resulted (1) from combining, in the Table 2 analyses, cigarette smoke exposure and atopy each with nasal congestion, which *was* strongly associated with PMEE, and (2) from not having separated, in the Table 1 analyses, smoking from nasal congestion, or atopy from nasal congestion.

We do not believe that evidence presented by Kraemer et al establishes either cigarette smoke exposure or atopy as risk factors for PMEE.

Kenneth D. Rogers, MD
Jack L. Paradise, MD
Charles D. Bluestone, MD
University of Pittsburgh
School of Medicine

1. Kraemer MJ, Richardson MA, Weiss NS, et al: Risk factors for persistent middle-ear effusions: Otitis media, catarrh, cigarette smoke exposure, and atopy. *JAMA* 1983;249:1022-1025.

In Reply.—The letter by Rogers et al details their objections to our analysis of the risk factors for persistent middle ear effusions. They claim that because household cigarette smoke exposure and an atopic history seem to be strongly related to nasal congestion, which in turn is strongly related to PMEE, the apparent associations of PMEE with cigarette smoke exposures and atopy are only artifactual. They support their assertion by noting that, when the data from Table 2 are adjusted for the presence of nasal congestion, there is then no difference in the proportion of cases and controls who were atopic or exposed to cigarette smoke.

However, we believe that it is *inappropriate* to control for nasal congestion when assessing the risk for PMEE associated with exposures to household cigarette smoke and with atopy. This is because of our feeling that nasal congestion should not be considered as a confounder in this instance but rather as a means by which the adverse effect of atopy or smoke inhalation on the development of PMEE is mediated. If nasal congestion is not a determinant of household cigarette exposure or atopy but is actually a consequence of their actions, controlling for this variable will spuriously reduce the relative risk associated with cigarette smoke exposures and atopy by forcing cases and controls to be artificially similar with regard to these factors.[1]

Thus, we contend that our original analysis was correct and that the results of our study support the hypothesis of an etiologic role for atopy and cigarette smoke exposure in the development of PMEE.

Michael J. Kraemer, MD
N. S. Weiss, MD
Seattle

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Association Between Smoke Exposure, Nasal Congestion, and PMEEs*

	Nasal Congestion Present		Nasal Congestion Absent	
	PMEE (%)	Control (%)	PMEE (%)	Control (%)
Smoke exposure	24 (73)	9 (27)	14 (38)	22 (61)
No smoke exposure	21 (68)	10 (32)	17 (33)	35 (67)

*PMEE indicates persistent middle-ear effusion.

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Black, Nick "The aetiology of glue ear-a case-control study" International Journal of Pediatric Otorhinolaryngology 9: 121-133, 1985.

This case-control study was designed to investigate the possible causes of glue ear (otitis media) in childhood. One hundred and fifty cases with two matched controls each made up the study population. Five factors were found to increase the risk of a child's undergoing surgery for glue ear: 1) parental smoking; 2) the child's mother being employed outside the home, but only if the father is employed in non-manual work; 3) attending pre-school day-care; 4) having an older sibling who had been diagnosed as suffering from glue ear; and 5) having been born locally. The author found that only one of these factors, parental smoking, appeared to be related to the actual development of glue ear. The other four factors were reportedly found to be related only to the chances of glue ear being detected in the child.

The children studied in this investigation were aged 4-9 years and had undergone a first operation for glue ear within the previous 30 months at the Radcliffe Infirmary in Oxford and was a resident of Oxford. The parents of these children were interviewed to obtain data on their child's medical, birth, family and social histories. Each of the cases was matched with two controls. One control was a child matched on age and sex who had attended a follow-up outpatient appointment in the general surgical or orthoptic departments. The second control was a child matched on age and sex from the same school class who was also the next child alphabetically of the same sex on the class roster.

(2) July

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The aetiology of glue ear — a case-control study

Nick Black

Department of Community Medicine and General Practice, University of Oxford, Oxford (U.K.)

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Key words: glue ear – etiology

Summary

A case-control study was carried out to investigate many of the proposed causes of glue ear in childhood. One hundred and fifty cases with two matched controls were found to be remarkably similar in nearly all medical and social aspects of their past and present lives, thus providing no support for many of the currently held views on the aetiology of glue ear. Of the 5 factors which were found to increase the risk of a child undergoing surgery for glue ear, only one of these is thought to be related to the development of the condition rather than to the chances of its detection. This factor was parental smoking (RR 1.64). The 4 other risk factors appear to influence the chance of glue ear being detected, diagnosed and referred for surgical treatment - the child's mother being employed outside the home, but only if the father is employed in non-manual work (RR 3.0); attending pre-school day-care (RR 2.00); having an older sibling who had been diagnosed as suffering from glue ear (RR 1.84); and having been born locally (in Oxfordshire) (RR 1.89). Possible explanations for these social and behavioural factors are discussed.

Introduction

Glue ear (also known as serous or secretory otitis media) is a condition in which non-purulent fluid accumulates in the middle ear causing some conductive deafness. Children with glue ear often also suffer from recurrent attacks of acute otitis media (AOM). Although it is a widely held view that AOM may lead to glue ear [25,35].

Correspondence: District Department of Community Medicine, Oxfordshire Health Authority, Manor House, Headley Way, Headington, Oxford OX3 9DZ, U.K.

there is considerable evidence that glue ear predisposes to AOM [17,23]. Glue ear is currently the commonest reason for surgery during childhood [4], the peak ages in the UK being 5–8 years of age. Although the condition has been recognised since at least the middle of the nineteenth century, there is no general agreement as to its cause. There have, over the past one hundred years or more, been many aetiological theories which have been extensively reviewed elsewhere. The large number of diverse factors that have been considered means that further investigation of this subject is well suited to a case-control study design. The study described here attempts to examine many of the existing claims about aetiology, and to assess some previously unconsidered factors [6].

Amongst the existing claims are those with some scientific support (living in a damp, humid climate [38,40]; parental smoking [21]; being first born in a family [14]); some of indeterminate status (overcrowding [9,16,27,39]; low socioeconomic status [14,27,36]; day care attendance [14,36,39]; an allergic predisposition [7,12,14,18,28,39]); and some without support or as yet unevaluated (effects of heredity [10,39]; acute exanthemata [15,39]; infant feeding [3,13,21,30]; air travel [22,29,41]). New areas of interest considered are family characteristics (such as parental ages and work status; sexes of siblings); educational achievement of parents; ante-natal and delivery events; exposure to vaccines and X-rays; and contact with animals.

There are 3 other factors which have been suggested, the investigation of which is not suited to a case-control study design. These are air pollution [9,15]; as a consequence of the misuse of antibiotics for AOM [2,10,22,43,44]; and the failure to perform sufficient adenotonsillectomies in children [11,20,24,27,29,31,43]. Studies which have considered these theories have failed to provide any support for them [6].

Method

Study design

Between May 1981 and October 1982, the parents of each child aged 4–9 years who had undergone its first operation for glue ear within the previous 30 months in the ENT department, Radcliffe Infirmary, Oxford and was resident in Oxfordshire, were interviewed and asked about their child's medical, birth, family and social histories. For each case two controls were selected–the 'hospital' control from children attending a follow-up outpatient appointment in the general surgical or orthoptic departments (Table I) and the 'home' control from the same school class (the next child alphabetically, of the same sex). The controls matched the cases with respect to sex and age (hospital controls within 6 months; home controls within 12 months). The parents of cases and hospital controls were interviewed, using a structured questionnaire, by the author in the respective outpatient departments. Parents of home controls were interviewed by one or other of two research interviewers in the controls' own homes.

Surgery for glue ear was defined as myringotomy (with or without insertion of tympanostomy tubes) with or without adenoidectomy. The contents of the middle-ear

TABLE I

DIAGNOSES IN 150 MATCHED HOSPITAL CONTROLS

Strabismus	57	Undescended testes & hydrocoele	20
Amblyopia	7	Phimosis	17
Hypermetropia/Myopia	6	Abdominal hernias	9
Reduced visual acuity	6	G.I.T./G.U. conditions	6
Refraction errors	6	Cysts, pilonidal sinus	5
Ptosis	1	Others	10
	83		67

on operation were noted as 'dry', 'serous fluid' or 'glue'. Children with cleft-palate were excluded as this condition has been clearly shown to be associated with glue ear [33].

Subjects

The parents of only one potential case and 3 potential hospital controls declined to participate due to lack of time for the interview. The parents of potential home controls were approached for 146 of the cases (4 of the cases having left the District by that time). Of these, 13 (9%) declined to participate. A second potential control was successfully recruited in these instances. In two instances the potential home control's GP refused permission for inclusion in the study and another child from the same school class was obtained. Of the 146 controls finally identified and interviewed, four were withdrawn from the analysis as they had undergone surgery for glue ear.

The hospital controls were selected so that they would be comparable with cases as regards factors affecting health service usage, and the home controls for factors affecting accessibility and availability of services. Thus, if the frequency of a factor differs between cases and both sets of controls, this suggests the factor is specifically related to children undergoing surgery for glue ear. On the other hand, if the difference is only between cases and home controls (with no difference between cases and hospital controls), this suggests the factor is associated with children undergoing hospital care in general (and not specifically related to children with glue ear).

Statistical methods

The results are first presented as simple contingency tables that take no account of the matched design of the study. The two control groups are displayed separately because of the different selective biases operating on each. In addition, data obtained about the home controls are subject to information bias arising from the different interviewer and interview situation. Risk ratios for all variables were estimated (unmatched ratio of cross-products) and their significance tested (by computing a χ^2 value). Statistically significant variables ($P < 0.05$) were further examined to take account of possible confounding (using the Mantel–Haenszel method of stratification). The original data concerning these variables were re-

analysed taking into account the matched study design. 95% confidence limits and significance testing (McNemar Test) for matched relative risks were computed.

Results

The respondents were mostly mothers (82%); of the remainder 5–6% were fathers, 11% were both parents, and 1% other relatives. There was no difference in this respect between cases and controls.

Of the 150 cases, 51 (34%) were aged 4 years–5 years 11 months; 69 (46%) 6 years–7 years 11 months; and 30 (20%) 8 years–9 years 11 months; 88 (59%) were male and 62 (41%) female. The age and sex distribution of this sample is similar to that for cases in the whole of Oxford Region (1975–1980). The same was true of the social class distribution (as determined by the father's occupation at the time of birth of the case).

Parents and siblings

The mean ages of both the fathers and the mothers of cases were similar to those

TABLE II

FAMILY MEMBERSHIP AND STRUCTURE OF CASES AND CONTROLS

	Cases	Hospital controls	Home controls
Parents' ages—Father *	36.5 ± 0.5	36.4 ± 0.6	36.6 ± 0.5
(mean ± S.E.M.)—Mother	32.5 ± 0.4	32.7 ± 0.4	33.5 ± 0.4
	No. (%)	No. (%)	No. (%)
Parental relationship **			
Together	143 (96)	135 (90)	130 (91)
Separated	7 (4)	15 (10)	12 (9)
Number of children			
1	9 (6)	18 (12)	9 (6)
2	84 (56)	80 (53)	82 (58)
3	40 (27)	39 (26)	33 (23)
4 or more	17 (11)	13 (9)	18 (13)
Birth order of subject			
1	63 (42)	69 (46)	58 (41)
2	67 (45)	57 (38)	55 (39)
3 and subs.	20 (13)	24 (16)	29 (20)
Sex of older siblings			
Male	62 (56)	52 (47)	59 (48)
Female	49 (44)	59 (53)	63 (52)

N.B. Differences not significant ($P < 0.05$) unless indicated.

* The term 'father' is used to designate the male head of household and includes stepfather, and mother's common-law husband

** The term 'together' describes all instances of the subject having always lived with the same two adults (including subjects adopted at a young age). 'Separated' includes all others (e.g) single parent families, step-parents etc.

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TABLE III

PARENTS' PAST AND PRESENT OCCUPATIONS'[6] AND COMBINATIONS OF PARENTAL WORKING STATUSES

NM, non-manual (Registrar General S.C.I. II. IIIN); M. manual (R.G.S.C. IIIM. IV.V).

	No. (%) of cases	No. (%) of hospital controls	No. (%) of home controls
Occupation at birth of subject			
Father -NM	60 (41)	68 (46)	65 (48)
-M	85 (59)	79 (54)	70 (52)
Parental work combinations			
Father (NM) -mother working	33 (56) *	23 (37)	42 (60)
-mother not working	26 (44)	40 (63)	28 (40)
(M) -mother working	37 (47)	37 (49)	33 (49)
-mother not working	42 (53)	39 (51)	35 (51)

N.B. Differences not significant ($P < 0.05$) unless indicated.

* $P < 0.05$ (comparison with hospital controls only)

of the parents of both sets of controls (Table II). A higher proportion of the older siblings of cases were male (though this was not statistically significant (n.s.)) and for all other measures of family structure only slight differences were observed. The length of parental full-time education and educational qualifications were remarkably similar between the 3 groups.

There was no significant difference between the proportions of fathers engaged in manual occupations (Table III). However, mothers of cases with work outside the home tended to be engaged in non-manual rather than manual work compared with the mothers of both controls. Any association with the working status of mothers was confined to the wives of non-manual men, and then only when compared with hospital controls ($P < 0.05$).

Preconception, pregnancy and perinatal events

Fewer of the parents of cases had used contraception during the year preceding the subjects conception, though this difference was not significant. Apart from this observation, the preconception period for the 3 groups were similar. No differences were observed for antenatal events (raised B.P., anaemia, antepartum haemorrhage, influenza, rubella). Exposure during pregnancy to both medical factors (scans, drugs, X-rays and amniocentesis) and non-medical factors (smoking, food fads) was similar. Data on the place of delivery, type of delivery, gestation, birth-weight and admission to a special care baby unit were also similar for the 3 groups. Proportions of infants breast-fed and the duration of breast feeding showed little difference.

Childhood medical history and exposure to medical procedures

There were no significant differences between the groups in the proportion with a history of allergic manifestations or having contracted the common infectious

TABLE IV

CHILDHOOD HISTORY OF ALLERGY, INFECTIOUS DISEASES AND EXPOSURE TO VACCINES, X-RAYS AND DAY-CARE

	No. (%) of cases	No. (%) of hospital controls	No. (%) of home controls
Allergic conditions			
Infantile eczema	15 (10)	18 (12)	19 (13)
Hay fever	15 (10)	14 (9)	15 (11)
Asthma	7 (5)	4 (3)	3 (2)
Sensitivity to food/drugs	23 (15)	17 (11)	16 (11)
Infectious diseases			
Measles	34 (23)	39 (26)	28 (20)
Mumps	57 (39)	52 (35)	55 (39)
Chicken-pox	80 (54)	74 (50)	96 (68)
Rubella	45 (30)	51 (34)	36 (25)
Whooping cough	11 (7)	16 (11)	14 (10)
Immunizations			
All routine schedule	93 (63)	82 (55)	92 (65)
Pertussis	107 (71)	92 (61)	105 (74)
Measles	136 (91)	135 (90)	125 (88)
Additional non-schedule [1]	10 (7)	11 (7)	10 (7)
X-ray exposure			
Dental	11 (7)	13 (9)	N.A.
Head and neck	21 (14)	23 (15)	21 (15)
Day-care attendance [2]			
nil or low	20 (13)	35 (23)	26 (18)
medium/high	130 (87) *	115 (77)	116 (82)

N.B. Differences not significant ($P < 0.05$) unless indicated.

* $P < 0.05$ (only compared with hospital control).

[1] Additional tetanus, BCG, smallpox, TAB, cholera.

[2] Day-care = (av. No. of hours per week × No. of months attended).

diseases of childhood (Table IV). Exposure to the routine immunizations and to X-rays was also similar in the three groups. Comparison of the amount of pre-school day-care attendance showed cases had attended more than controls ($P < 0.05$ when compared with hospital controls).

ENT histories of parents and siblings

Parental history of having undergone tonsil and/or adenoid surgery showed remarkable similarity between the groups, with the proportion of mothers considerably higher than fathers (Table V). A higher proportion of the siblings of controls had a history of recurrent acute otitis media and recurrent tonsillitis ($P < 0.05$). In addition, if older siblings only are considered, a higher proportion of those of cases had a history of glue ear. The older siblings of cases with glue ear were more likely to have been referred to ENT departments and treated surgically, than the older siblings of controls, though this difference did not achieve statistical significance.

TABLE V

ENT HISTORIES OF PARENTS AND SIBLINGS

	No. (%) of cases	No. (%) of hospital controls	No. (%) of home controls
Parental history of Ts and As [1]			
Father	40 (28)	40 (29)	38 (27)
Mother	62 (42)	60 (40)	50 (36)
Sibling history of ENT problems	(n = 210)	(n = 208)	(n = 211)
Recurrent A.O.M. [2]	42 (20) *	62 (30)	72 (34)
Recurrent tonsillitis	30 (14) *	45 (22)	41 (19)
Glue ear	26 (12)	16 (8)	17 (8)
Sibling treatment for glue ear	(n = 26)	(n = 16)	(n = 17)
Referral to ENT	22 (85)	12 (75)	12 (70)
Surgery	19 (73)	9 (56)	10 (59)
Older siblings history of ENT problems	(n = 84)	(n = 81)	(n = 84)
Recurrent A.O.M.	19 (23) *	31 (38)	33 (39)
Recurrent tonsillitis	19 (23) *	34 (42)	29 (35)
Glue ear	19 (23) **	8 (10)	14 (17)
Older siblings treatment for glue ear	(n = 19)	(n = 8)	(n = 14)
Referral to ENT	18 (95)	5 (63)	9 (64)
Surgery	16 (84)	5 (63)	8 (57)

N.B. Differences not significant ($P < 0.05$) unless indicated.
* $P < 0.05$ (compared with hospital and home controls).
** $P < 0.05$ (compared with hospital control only).
[1] Tonsillectomy and adenoidectomy.
[2] Acute otitis media.

Home environment

Most aspects of housing conditions showed great similarity. These included the type and age of the accommodation, the occupying basis (owned, rented, tied), density of occupation and the basic amenities (bath/shower, washing machine, telephone, refrigerator). The exception to this was that a higher proportion of case

TABLE VI

FAMILY MOBILITY DURING SUBJECT'S LIFETIME

	No. (%) of cases	No. (%) of hospital controls	No. (%) of home controls
Residence at time of subject's birth			
Oxfordshire	123 (82) *	107 (71)	106 (75)
Elsewhere	27 (18)	43 (29)	36 (25)

N.B. Differences not significant ($P < 0.05$) unless indicated.
* $P < 0.05$ (only compared with hospital controls).

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families reported using an 'unsealed' heating system, that is, a system that emits the products of combustion (open fires, gas fires, paraffin stoves) ($P < 0.05$).

A higher proportion of the families of cases were already living in Oxfordshire when the subject was born, than was true for the controls ($P < 0.05$) (Table VI). Other measures of geographical mobility showed no difference. Other factors examined which also showed no difference included air travel by the subjects, possession of pets, and regular contact or close proximity to farm animals.

Smoking habits of household members

The present smoking status of the parents (smoker, ex-smoker, never-smoked) showed a small and insignificant difference between cases and controls. A smoking rate was calculated based on the number of years of the subjects life that the household member had smoked for, and the daily number of cigarettes smoked (or cigarette equivalent in the case of cigar and pipe smokers). This revealed that a slightly higher proportion of cases had been exposed to medium/high levels of smoking than had controls, but this difference failed to achieve statistical significance.

Confounding and matched analysis

The relative risks (RR) for all variables included in Tables II–VI were estimated by comparison with hospital controls and with home controls. For all but one variable the R.R. based on comparison with the hospital control was similar to that based on comparison with the home control (the exception was the effect of the mother working outside the home). Variables with RRs which proved to be statistically significant ($P < 0.05$), plus that for parental smoking habits, are shown in Table VII. These variables were further examined for evidence of confounding. The

TABLE VII

RELATIVE RISKS OF GLUE EAR BASED ON UNMATCHED COMPARISON WITH HOSPITAL CONTROLS [a], AND HOME CONTROLS [b]

Variable	R.R. [a]	R.R. [b]
Working mother	1.41	0.89
with N.M. father	2.16 *	0.85
Day-care attendance		
medium/high	2.00 *	1.47
Siblings with glue ear		
older siblings only	2.54 *	1.81
Smoking rate		
household	1.45	1.28
Residence		
born in Oxon	1.86 *	1.52
Unsealed heating system	1.59 *	1.59 *

N.B. Differences not significant ($P < 0.05$) unless indicated.
* $P < 0.05$.

TABLE VIII

RELATIVE RISKS OF GLUE EAR BASED ON MATCHED COMPARISON WITH HOSPITAL CONTROLS [a], AND HOME CONTROLS [b]

Variable	R.R. [a]	95% conf. limits	R.R. [b]	95% conf. limits
Working mother	1.36	-	0.94	-
with N.M. father	3.00 *	1.15–7.80	0.89	-
Day-care attendance (med/high)	2.00 +	1.13–3.53	1.50	-
Older siblings with glue ear	1.84 *	1.01–3.37	1.64 *	1.06–2.55
Smoking rate household	1.64 *	1.03–2.61	1.52 *	1.06–2.21
Residence born in Oxon	1.89 +	1.11–3.21	1.88 *	1.07–3.29

N.B. Relative risks not significant ($P < 0.05$) unless indicated.
* $P < 0.05$; + $P < 0.02$; (McNemar test).

only factor for which the estimate of RR was the result of confounding was unsealed heating (when parental smoking and birth in Oxfordshire were taken into account).

The other variables were re-examined by matched-pair analysis (Table VIII). This revealed similar findings to those from unmatched analysis (Table VII) for cases and both sets of controls, apart from parental smoking, for which the RR became significant on matched analysis. The data were further analysed on the basis of the contents of the middle-ear as found at operation. Of the 150 cases, 106 were found to have thick mucoid 'glue' in at least one ear, whilst the remaining 44 had either thin serous fluid or no fluid at all. Estimates of relative risk based on matched analysis of only those with 'glue' revealed similar findings to analysis of the complete series.

Discussion

The main methodological problem encountered was the selection of controls. There was no ideal group of hospital patients from which to choose—those selected were the most appropriate available. As regards home controls, possible bias arising from different interviewers in a different setting from cases and hospital controls is considered to have had only an insignificant effect. This can be judged by the similarity of the relative risks obtained by comparison with each set of controls.

The size of this study means that risk factors present in 50% of controls would have a 90% chance of being detected if the relative risk associated with them was at least 2.0. However, the relative risk would have to be at least 3.5 if the factor was present in only 5% of controls. Negative findings must be interpreted in this context. The most striking finding was the similarity between cases and controls, or, to put it another way, how remarkably ordinary children with glue ear appeared to be in

nearly all aspects of their past and present lives. There were, however, a few exceptions.

(a) Climate

Evidence for the effect of humidity and altitude is difficult to obtain in a localised study of this design. Oxfordshire has a local reputation as having a high prevalence of glue ear attributed to the effect of the Thames Valley, and indeed, cases were found to be associated with having been born in Oxfordshire (RR 1.89; $P < 0.02$). While local climatic conditions could be responsible for such a finding, many other environmental factors could also be implicated.

(b) Socio-economic conditions

Previous studies of the influence of social class have failed to demonstrate any association with glue ear [27,34,36,39,42]. This was true of this study. There is, however, no reference in the literature to the influence of mothers working outside the home, a factor that appeared to be associated with glue ear (Table VIII), compared to hospital controls, if the father was employed in non-manual work (RR 3.0; $P < 0.05$). However, this association with mother's employment status was not observed in comparison with home controls. There are 3 possible explanations for this difference–the association is due to chance; the risk estimate from the hospital control analysis may reflect a relative 'lack' of occupation outside the home for control mothers rather than an 'excess' for case mothers; or, information bias associated with the home interview may have led to 'over-recording' of maternal occupations by the mothers of home controls. It is not apparent from the data which of these explanations is correct. The only related information, on parental education, showed no associations with glue ear in the child.

A possible explanation for the association between glue ear and maternal employment status, where the father is employed in non-manual work, may be the family's attitude to the mother working. Wives of non-manual husbands are perhaps less likely to work for primarily financial reasons than the wives of manual men. Working for other reasons (e.g. career oriented; psychological benefits of getting out of the home) may be associated with attitudes to health and illness that differ from the attitudes of non-manual families in which the mother does not work. In turn these attitudes may be associated with tl detection of glue ear and obtaining surgical treatment. In other words, the risk associated with mothers working may be explained in terms of health behaviour, rather than in terms of disease aetiology. Investigation of the effect of housing conditions has produced conflicting results in the past [9,15,16,39]. There was no clear evidence of housing conditions influencing the occurrence of glue ear in this study.

(c) Family history

It is difficult to obtain reliable information on the history of glue ear in parents due to the frequent changes of name the condition has undergone. If parents had suffered from glue ear, severely enough to necessitate surgery, then they would, on average, have been treated in the 1940s. At this time surgical treatment would have

involved adeno-tonsillectomy. There was no difference in the history of this operation between case and control parents (Table V).

The siblings of cases were more likely to have been diagnosed as suffering from glue ear than the siblings of controls (RR 1.84; $P < 0.05$). Conversely, a history of recurrent acute otitis media (AOM) was commoner in the siblings of controls. If these two middle-ear conditions are considered together, then any association between middle-ear disease in siblings and glue ear in the subject disappears (RR 0.77). Whilst not all children with a history of recurrent AOM have glue ear, the clinical distinction between the two is often not clear [17,23,25,35]. The initial diagnosis of glue ear is usually made by a General Practitioner, who, in negotiation with the parents, decides whether or not to refer the child for specialist attention. With over 200 GPs referring to the ENT department in this study, it would be expected that a wide range of indications for referral were being practiced. In this way, a child with a sibling with glue ear would be more likely to also be diagnosed as glue ear (rather than recurrent AOM) than a child without a 'glue ear' sibling (assuming all children from the same family attend the same GP with the same parents). This is supported by the finding that siblings of cases diagnosed as having glue ear are more likely to be referred to ENT care and be managed surgically than siblings of controls (Table V).

The risk associated with a sibling with glue ear therefore appears to be a product of the behaviour of parents and health care professionals, rather than any 'true' hereditary effect, though this requires further investigation. This is consistent with the only recently published study which has examined this factor [39].

(d) Subjects medical history

No association was found between any aspects of the subject's past medical history and the occurrence of glue ear. These aspects included infant feeding, common infectious diseases and allergic conditions. This study confirms the findings of several others that demonstrated the proportion of glue ear cases with a history of allergy was similar to the prevailing frequency in the general population [8,19,26,38].

(e) Behaviour

A significant association was found (RR 1.64; $P < 0.05$) between glue ear and the smoking habits of all household members throughout the subject's life. This analysis assumes a constant level of exposure to smoke throughout the subject's life. Further study would be required to determine whether or not the risk of smoke is associated with any particular stage of childhood. This finding is consistent with a recent study in the USA [21] and other evidence about the hazards of passive smoking [1].

The reported risks of exposure to pre-school day-care have been conflicting [3,14,39]. This study suggests day-care attendance is a risk (RR 2.00; $P < 0.02$), though the mechanism is unclear. Day-care may increase the likelihood of a child acquiring a middle-ear infection and subsequently being examined for evidence of glue ear, or the day-care staff may be on the lookout for evidence of glue ear and proceed to alert unsuspecting parents.

In conclusion, while this study has failed to substantiate the role of many

biological factors in the aetiology of glue ear (with the exception of tobacco smoke). It has suggested that social and behavioural factors may be at least as, if not more, important in determining which children are detected, diagnosed and treated surgically for glue ear. The influence of such factors requires further investigation to support such a claim.

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Moorhead, Robert "Passive smoking and young children's health" Australian Family Physician 14(10): 1058-1062, 1985.

This article is based on a general practice study. The aim of this study was to determine whether the children of smoking parents in this population have different morbidity patterns in their visits to a general practitioner. The eighteen month investigation examined the families of 170 children from 0-5 years of age. Families were matched for age, sex, social class and size. The author reports that the smoking group children "attended more frequently, had more diagnoses per consultation and spent more days in hospital" than the non-smoking group children. The diseases that were reportedly associated with parental smoking in this study were otitis media, upper and lower respiratory disease, conjunctivitis, infectious disease and accidents. There were several conditions which were found not to be associated with parental smoking in this study such as croup, skin disease, rubella, and modified pertusis.

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SPECIAL FEATURE

Passive smoking and young children's health

Robert Moorhead

Recent international studies have been documented which suggest a link between passive smoking and disease in young children. They include studies of passive smoking and its relationship to pneumonia and bronchitis,[1,2] respiratory disease,[3] *restricted activity due to acute respiratory disease,*[4] *increased winter admissions*[5] *and increased visits to doctors.*[6] *This article is based on a general practice study in this area.*

The aim of this study was to see if children of smoking parents have different morbidity patterns in their visits to a general practitioner. The 24 categories of health problems studied are as follows:

- Total consultations
- Total diagnoses (all diagnoses were by encounter)
- Winter consultations
- Spring consultations
- Summer consultations
- Autumn consultations
- Respiratory diagnoses
- Preventive classification diagnosis
- Nervous and sense organ diagnoses
- Skin diagnoses
- Trauma diagnoses
- Upper respiratory tract infection and pharyngitis
- Tonsillitis diagnoses
- Wheezing — patient initiated diagnoses
- Wheezing — total diagnoses
- Vaccinations
- Gastroenteritis diagnoses
- Rubella diagnoses
- Scarlet fever diagnoses
- Modified pertussis diagnoses
- Conjunctivitis diagnoses
- Otitis media diagnoses
- Hospital admission — number of days
- Infectious disease diagnoses.

Robert G Moorhead, MB, BS, FRACGP, DCM, is in solo general practice in Kambah, near Canberra and has an ongoing interest in general practice research.

The study began on 1 January 1979 and ran for 18 months. Regular attenders of the author's practice were selected because some families used more than one doctor. This ensured that subsequent morbidity was being presented to the recorder only. All practice records were studied and families were selected, with married parents (under 45 years of age), in which every member had attended the practice at least once in the past two years. From this group of families 170 children, from newborn to the age of five years, were identified. Their parents' smoking habits had been recorded previously and the children were divided into two groups: one or both parents smoking; or neither smoking.

Families were matched for age, sex, social class[7] and size (greater than two, or two or less children) using punch cards. As with all matching procedures, not all children could be matched so the study started with 106 children — 53 in each group. This was a non randomised cohort study.

The morbidity recorded fulfilled the definitions in the International Classification of Health Problems in Primary Care (ICHPPC).[8] The diagnoses were studied according to age group.

The practice after hours work is performed by a locum service run by the principals and a written report was available on such diagnoses. All in-patient hospital records for patients in this survey were studied by the author and the number of days in hospital recorded. Home visits, after hours visits and consultations were included in the survey.

There were two outcomes measured in the study. One was the chi-square on the 24 items of morbidity for both groups, which was calculated by computer. The other was the mean of the diagnoses for the smoking and non smoking group.

The smoking group children attended more frequently, had more diagnoses per consultation and spent more days in hospital.

Table 1 shows the common diagnoses for the two groups and the predominance in the smoking group for certain diagnoses. In *Table 2* less common diagnoses and other health problems are recorded. There was a similar finding for total wheezing (initial and doctor requested follow up). Days in ACT hospitals were defined as the calendar difference between dates of admission and final discharge, midnight to midnight.[9] The mean of the number of days spent in hospital by those in the smoking group was nearly double that of those in the non smoking group. It is interesting that more vaccinations were performed for the smoking group.

Not every rubric studied produced a greater number of diagnoses for the children of smoking parents. For example there were 27 diagnoses of croup and 16 of these occurred in the non smoking group. Skin disease results were similar, 24 to 39, as were those of rubella and modified pertussis. No child in the survey died but a baby born to a family whose sibling was in the study died from Sudden Infant Death Syndrome. Both parents of this baby smoked.

Using chi square, all the data for the

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Table 1 Common diagnoses		
Disease/health problem	Parent(s) smoking	Parents non smoking
Winter consultations	172	138
Spring consultations	107	82
Summer consultations	48	45
Autumn consultations	71	39
Respiratory diagnoses	218	154
Nervous and sense	104	63
Infectious disease	68	34
Preventive	40	28
URTI, pharyngitis	125	95
Otitis media	80	49
Gastroenteritis	37	17
Total diagnoses	502	372
Total consultations	398	306

URTI: upper respiratory tract infection

Table 2 Further diagnoses and health problems		
Disease/health problem	Parent(s) smoking	Parents non smoking
Days in ACT hospitals	80	41
Wheezing on auscultation (total)	45	32
Wheezing on auscultation (initial)	28	17
Vaccinations	39	20
Conjunctivitis	15	7
Trauma	13	9
Tonsillitis	9	6
Scarlet fever	8	2

ACT: Australian Capital Territory

24 categories were studied — there were 2,243 observations for the smoking group and 1,614 for the non smoking. Chi square equalled 36.34 with 24 degrees of freedom and the probability level (p) equals 0.0509, which is almost significant at the five per cent level. However, there were five cells with expected frequencies less than five (these were for both groups in rubella, the non smoking group in scarlet fever and both groups in modified pertussis). If these rows are omitted chi square equals 34.91 with 22 degrees of freedom and p equals 0.0396 which is significant at the five per cent level. If the rows were combined then chi square equals 33 and p equals 0.0619 which is significant at the 10 per cent level.

The means of the diagnoses per patient over 18 months were calculated. *Figure 1* shows a greater mean of consultations (7.6 to 5.9) and diagnoses (9.6 to 7.0) for the children of smoking parents. Breaking consultations and diagnoses into age groups showed a continuing dominance of the smoking group in all ages except for age two to three years. *Figure 2* shows the breakdown of total consultations by season with smoking group dominance in all seasons but especially in autumn. Breaking down winter and spring consultations by age showed the smoking group again ahead in all ages except for age two to three years. *Figure 3* compares the means of

The smoking group children had more diagnoses of respiratory disease, nervous and sense organ disease, trauma and infectious disease.

diagnoses per patient for the larger classifications of illnesses. The smoking mean was higher for respiratory (4.2 to 3.0), nervous and sense organ, infectious, preventive and accident groupings but not for skin disease. For the ICHPPC — 2 rubrics (*Figure 4*), the

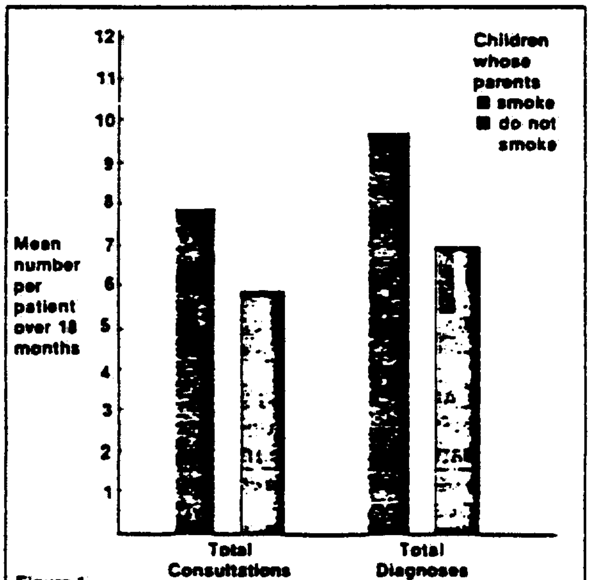

Figure 1

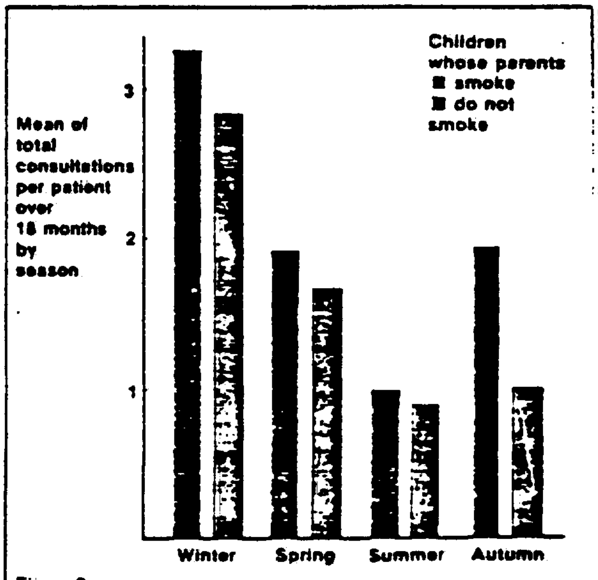

Figure 2

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means were URTI, pharyngitis (2.4 to 1.8), otitis media (1.5 to 0.9), vaccinations (0.8 to 0.4) and gastroenteritis (0.7 to 0.3). In each of these categories the smoking group showed more diagnoses.

Discussion

Parental anxiety was a variable which was not included in the matching procedure. It may have played an important role as smokers exhibit more neurotic symptoms than non smokers[10] and it may be this factor that drives the smoking parents to consult the doctor with their children. [redacted] These are similar findings to previous studies on the effects of smoking. The greater number of tonsillitis diagnoses in the smoking group correlate with another study which has demonstrated a higher rate of tonsillectomy in the children of smokers.[13]

Wheezing was a clinical measure[14] as airflow meters are difficult to use with young children. Other studies of older children have shown forced expiratory volume (FEV) changes directly related to the child's mother's smoking.[15, 16] [redacted]

The tracer disease otitis media was expected to express itself equally in both groups but it featured more prominently in the smoking group.

[redacted] Parental anxiety may be a factor here. Breast feeding has a protective effect and one asks, do breast feeders tend to be non smokers? Carbon monoxide poisoning can mimic gastroenteritis.[17] [redacted] This finding is supported by another study which showed sidestream smoke as a cause of measurable physical change to the tear film.[18]

The mechanism of disease production from cigarette sidestream smoke is unknown. [redacted]

The sample in this study had a similar general morbidity pattern to another group of children studied in a Newcastle practice several years ago.[23] Future studies should include the child minder's smoking habits as another variable and use tracers such as cotinine to detect the presence of 'passive' smoke. The study is limited to this sample and extrapolation of the findings cannot be made universally but they definitely indicate that further studies should be made. The age group involved (young children) constitutes an important part of primary

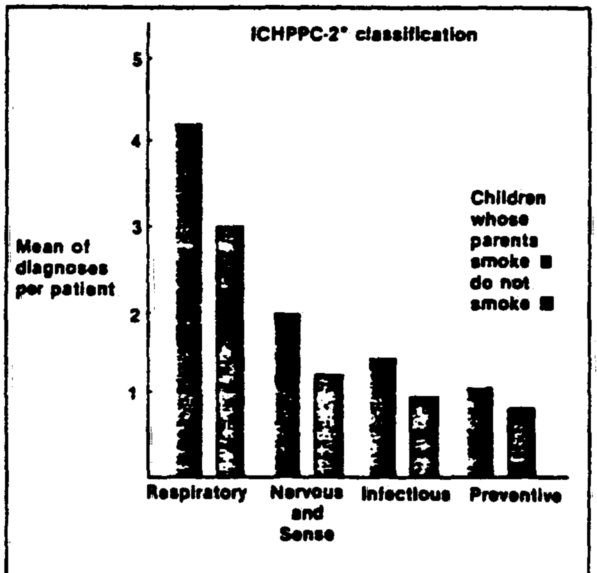

Figure 3

*International Classification of Health Problems in Primary Care

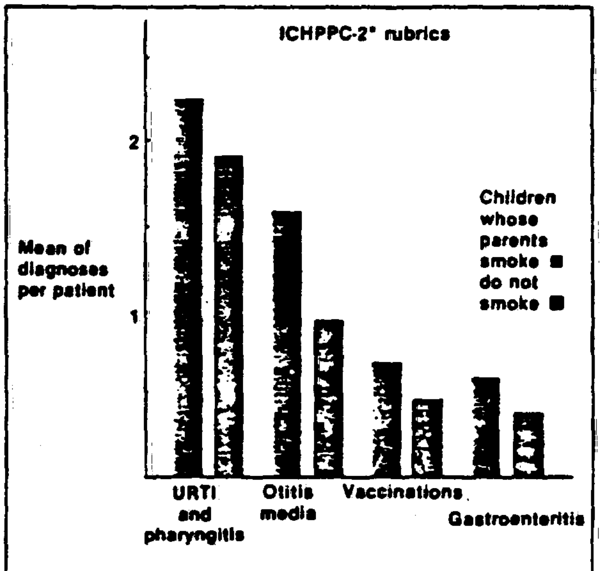

Figure 4

*International Classification of Health Problems in Primary Care.

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care in this country.[37] Many people, especially women, smoke at the time they begin their families and this group particularly should be encouraged by their general practitioners to give up smoking.[38]

Conclusion

There were differences between the smoking and non smoking groups in this sample, and overall, they were great enough to be almost significant at the five per cent level. Upper and lower respiratory disease, conjunctivitis, otitis media, infectious disease and accidents featured more strongly in the smoking group. One would expect the tracer disease — otitis media — to express itself equally in both groups, but in fact it featured more prominently in the smoking group. The smoking group consulted more and spent more days in hospital.[?] Larger studies in a primary care setting are strongly recommended.

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Reprint requests
Dr R G Moorhead
53 [illegible] Street
[illegible] 2902

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Pukander, J., Luotonen, J., Timonen, M. "Risk Factors Affecting the Occurrence of Acute Otitis Media among 2-3-Year-Old Urban Children" Acta Otolaryngol 100: 260-265, 1985.

ABSTRACT. The factors affecting the occurrence and recurrence of acute otitis media (AOM) were studied among 471 2-3-year-old children in two cities in Finland. Of these children, 188 had experienced $\geq$ 3 attacks of AOM, 76 had had 1-2 attacks and 207 no otitis attacks (=control group). The study showed that the risk of recurrent AOM was increased among those children attending day-care nurseries as well as among those who had several siblings. Proneness to rhinorrhea and exposure to passive smoking at home was associated with an increased risk of AOM, while prolonged breast-feeding (> 6 months) seemed to reduce it. No correlation was found between the risk of recurrent AOM and the place of residence or type of housing, the parental otitis history, or atopic diathesis of a child. Thus the study suggested that to protect a young child from AOM we should promote breast-feeding and home-care for babies as well as avoid smoking in the home.

Acta Otolaryngol (Stockh) 1985; 100: 260–265

Risk Factors Affecting the Occurrence of Acute Otitis Media among 2–3-Year-Old Urban Children

J. PUKANDER,[1] J. LUOTONEN,[2] M. TIMONEN[3] and P. KARMA[1]

From the [1]Department of Clinical Sciences, University of Tampere and the Department of Otolaryngology, Tampere University Central Hospital, Tampere, the Departments of [2]Otolaryngology and [3]Pediatrics, University of Oulu, Oulu, Finland

Pukander J, Luotonen J, Timonen M, Karma P. Risk factors affecting the occurrence of acute otitis media among 2–3-year-old urban children. Acta Otolaryngol (Stockh) 1985; 100: 260–265.

The factors affecting the occurrence and recurrence of acute otitis media (AOM) were studied among 471 2–3-year-old children in two cities in Finland. Of these children, 188 had experienced ≥3 attacks of AOM, 76 had had 1–2 attacks and 207 no otitis attacks (= control group). The study showed that the risk of recurrent AOM was increased among those children attending day-care nurseries as well as among those who had several siblings. Proneness to rhinorrhea and exposure to passive smoking at home was associated with an increased risk of AOM, while prolonged breast-feeding (>6 months) seemed to reduce it. No correlation was found between the risk of recurrent AOM and the place of residence or type of housing, the parental otitis history, or atopic diathesis of a child. Thus the study suggested that to protect a young child from AOM we should promote breast-feeding and home-care for babies as well as avoid smoking in the home. *Key words: middle ear, epidemiology, environmental factors.*

J. Pukander, Department of Otolaryngology, University of Tampere, SF-33520 Tampere, Finland.

Acute otitis media (AOM) is a very common affection among young children. Typical of the disease is a high incidence of recurrences, especially during the first few years of life (1, 2, 3). One reason for this is that the immunological defence mechanisms of a child mature relatively slowly during the first years of life (4) leaving a young child prone to infections. But environmental factors such as population density (5) and air pollution (6) have also been shown to affect the occurrence of AOM considerably.

The purpose of this study was to evaluate factors predisposing to recurrent AOM in a population of 2–3-year-old urban children in Finland.

MATERIAL AND METHODS

The patient material of the present study consisted of 264 consecutive 2–3-year-old children who visited, because of AOM (characterized by acute symptoms and effusion in the middle ear) the Out-Patient Department of Otolaryngology or Pediatrics of the University Central Hospitals of the cities of Tampere and Oulu in Finland. There were 120 girls and 144 boys. As a non-otitis control-group we took 207 children (106 girls, 101 boys) of the same age from the municipal children's health centres of the same two cities. The enrolment criterion was freedom from AOM thus far in life. The mean age of the otitis patients was 2.90 years and that of non-otitis controls, 3.09 years.

During the Out-Patient AOM visit, information regarding the number of attacks of AOM experienced thus far during the child's lifetime as well as epidemiologic data of interest for the study was obtained by means of a questionnaire to the parents of the otitic children. A

similar questionnaire was filled in by parents of non-otitic children in the children's health centres. The questionnaire comprised the following questions: The duration of breast-feeding, the day-case arrangements, the number of siblings and their otitis history, presence of allergic manifestations, occurrence of rhinorrhea and other respiratory infections, the otitis history and smoking habits of the parents and the family's place of residence.

To study the factors associated with AOM, the children were classified into three groups according to the otitis history (the questionnaire-visit included): no attacks (= control group, n=207) 1 or 2 attack(s) (n=76) and three or more attacks (n=188). For statistical analysis we used the χ^2-test.

RESULTS

Of all children, 91 had been cared for in day-care centres for more than a 6-month period (Table I). They were found to have had AOM significantly more often than children cared for at home, whereas day-care within the family did not increase the number of otitis attacks. Also, on the other hand, the number of siblings in a child's family affected the frequency of AOM almost significantly, so that greatest risk of repeated attacks was found among those children who were from families with three or more children (Table II).

In the present study neither the place of residence (within the city limits) nor the type of housing affected the risk of contracting AOM. Likewise, no correlation was found between the parental otitis history and the occurrence of AOM in the children.

Breast-feeding—and especially its prolongation for over 6 months—seemed to protect a baby against AOM, and a significant negative correlation was found between the duration of breast-feeding and the number of otitis attacks (Table III).

[redacted] to sensitize a child [redacted] (Table IV).

Furthermore, a highly significant correlation was found between the occurrence of rhinorrhea (as compared with its frequency in other children in the neighbourhood) and a liability to repeated otitis attacks (Table V).

Table I. *Day-care arrangements and occurrence of AOM*

	Day-care form[a]		
Number of attacks	Day-care[b] centre	Family[b] day-care (home)	Own home
0	28	41	133
1–2	16	15	45
≥3	47	35	102
Total	91	91	280

Significance of partitioned columns	χ^2	DF	p
Day-care centre vs. own home	8.486	2	0.014
Day-care centre vs. family care	4.237	2	0.120
Family care vs. own home	0.171	2	0.918

[a] Data not available from 9 children.
[b] Cared for ≥6 months outside own home.

16.6% of all the children showed some atopic manifestation; infantile eczema was found in 11.8%, asthma in 2.3% and hay-fever in 2.5%. No significant correlation was found between the allergic diathesis and the occurrence of AOM.

DISCUSSION

Because of the commonness of AOM (7) and the magnitude of human suffering and economic loss it causes, every effort must be made to reduce its frequency. Therefore epidemiological studies of the factors affecting the occurrence of (recurrent) AOM and the possible removal of these factors are of importance.

In the majority of cases, AOM is nowadays preceded by an upper respiratory viral infection (8, 9, 10, 11). One of the most outstanding manifestations of respiratory infection is rhinorrhea. In the present study, a close correlation was found between a proneness to rhinorrhea and the recurrence of otitis attacks. Although we did not distinguish between allergic and viral rhinorrhea, the finding might suggest that the mucosa of one part of the respiratory tract—the middle ear—reflects the changes of another part—the nose—regardless of the background of the damage.

Viruses tend to spread more easily, the higher the population density in a certain area. Thus the number of human contacts in a child's daily life plays a very important part in the

Table II. *Size of the family and occurrence of AOM*

Number of attacks	Number of siblings 0	1	≥2		
0	97	80	30		
1–2	30	35	11		
≥3	64	77	47		
Total	191	192	88		
Significance of partitioned colums			χ^2	DF	p
0 vs. ≥2			11.449	4	0.022

Table III. *Breast-feeding and occurrence of AOM*

Number of attacks	Duration of breast-feeding (months) <1	1–3	4–6	>6	
0	16	89	43	59	
1–2	11	32	15	18	
≥3	36	73	41	38	
Total	63	194	99	115	
Significance of partitioned colums		χ^2	DF	p	
<1 vs. 1–3		9.178	2	0.010	
<1 vs. 4–6		5.571	2	0.062	
<1 vs. >6		12.252	2	0.002	

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likelihood of contracting AOM. Day-care centres with many children in the same place create favourable conditions for respiratory epidemics (12), with AOM as a sequel. This is confirmed in our study by the children who attended day-care centres and who contracted AOM more frequently than children cared for in their own homes, a finding also consistent with some earlier reports (13, 14, 15, 16). The greater size of the family increases the number of daily human contacts of a child and may work analogously with the day-care. Accordingly, in the present study, the children from families with three or more children contracted AOM more frequently than children from smaller families. Cunningham (17) also stated that the presence of other children was associated with increased morbidity in respiratory infections, otitis media included. On the other hand, Watkins et al. (18) and Vinther et al. (19) did not find any correlation between the number of siblings and the frequency of AOM, and in the series of Paterson & MacLean (20) the non-otitis control children even belonged to larger families compared with children with AOM. Consequently, although the reports on the effect of family size on the liability of a child to contract AOM are not all in agreement, we strongly recommend that children should be cared for in small, separate, family-size groups (12) instead of large day-care centres.

Prolonged breast-feeding has been found to protect a baby against respiratory infections in general (18, 21). This is thought to be due to the transmission of specific human immunoglobulins in breast milk thus improving the immunological defence mechanisms of an infant (22, 23, 24). Furthermore, the immunoglobulins may also coat the bowel mucosa, thus preventing the absorption of harmful cow's milk proteins (25). In the present study,

Table IV. *Exposure to passive smoking and occurrence of AOM*

Number of attacks	Smoking of parents(s)	
	No	Yes
0	136	71
1–2	40	36
≥3	93	95
Total	269	202

Table V. *Rhinorrhea and occurrence of AOM*

Number of attacks	Occurrence of rhinorrhea compared with other children in neighbourhood*				
	Never	Less than in other children	Equally with other children	More than in other children	Continuously
0	18	75	112	2	0
1–2	3	13	53	6	0
≥3	0	9	128	37	10
Total	21	97	293	45	10
Significance of the whole contingency table		χ^2 119.99	DF 8	p <0.001	

* Data not available from 5 children.

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children who had been breast-fed for over 6 months experienced significantly fewer episodes compared with those breast-fed for less than 1 month. This is in accordance with reports indicating a lower recurrence rate of AOM among infants breast-fed over a relatively long period, i.e. 6–12 months (25, 26), and with the finding that infants breast-fed for less than 3 months experienced their first AOM significantly earlier than those breast-fed for longer periods (27). On the other hand, no significant correlation between the duration of breast-feeding and the liability to contract AOM was found by Kjellman (28) and Vinther et al. (19), probably because of the design of these studies. However, evidence strongly supports the advisability of breast-feeding, which in fact is becoming more fashionable again after a period of underrating this natural way of nourishment (18, 29, 30). This favourable development should be encouraged.

Parenteral smoking exposes the whole family to smoke and this "passive smoking" has been found to predispose children to respiratory infections (6, 31, 32, 33). Accordingly smoke must be a predisposing factor to AOM, too. However, as far as we know there are no earlier reports indicating an increased risk of AOM among children from smoking families. On the contrary, Vinther et al. (19) did not find any such connection, probably because of the masking effect of other parameters (e.g. day-care) in their study. The problem of passive smoking has become more important along with changes in housing, with increasingly more families living in cities in rather small flats, where the amount of indoor smoke reaches much higher concentrations, compared with old-fashioned farmhouses.

Opinions of the role of allergy in the etiology of AOM are not unanimous. In the present study no constant correlation was found between atopic diathesis of a child and the frequency of AOM, an observation also made by Kjellman (28). Many studies, however, have shown an association between atopic allergy and a tendency to recurrent or prolonged otitis, i.e. secretory otitis media (25, 34, 35), especially among children who also had a positive family history of allergy (36). On the whole, the role of allergy *per se* as a risk factor to AOM might not be to straightforward after all, and further studies are warranted to clarify this.

In conclusion, our study revealed that certain factors associated with the proness of small children to acute and recurrent otitis media can be regarded as a consequence of social and cultural changes. [redacted]

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Fleming, D.W., Cochi, S.L., Hightower, A.W., Broome, C.V. "Childhood Upper Respiratory Tract Infections: To What Degree Is Incidence Affected by Day-Care Attendance?" Pediatrics 79(1):55-60, 1987.

ABSTRACT: Risk factors for acute upper respiratory tract disease in childhood were evaluated in a population-based sample of the Atlanta metropolitan area. Mothers from 449 households containing 575 children less than 5 years of age were selected by random-digit dialing and questioned about upper respiratory tract infection and ear infection occurring in their children during the preceding 2 weeks. Household demographic and socioeconomic characteristics, maternal smoking history and child day-care attendance and breast-feeding information were also obtained. For children less than 5 years of age, the reported incidence of upper respiratory tract infection was 24%, and of ear infection, 6%. Controlling for the other variables measured, day-care attendance was associated with a significantly increased risk of both illnesses. For upper respiratory tract infection, increased risk was present for all children attending daycare ($P = .02$, odds ratio $= 1.6$), whereas for ear infection, risk could be demonstrated only for full-time attendees ($P = .005$, odds ratio $= 3.8$). Maternal smoking was a second independent risk factor for a child's having upper respiratory tract infection (odds ratio $= 1.7$, $P = .01$). Thirty-one percent of all upper respiratory tract infection among day-care attendees and 66% of all ear infections among full-time day-care attendees were attributable to day-care attendance. Given the proportion of children in day-care, 9% to 14% of the total burden of upper respiratory tract disease in this population was daycare related. As use of child day-care facilities has increased, this specific exposure has become a major factor contributing to transmission of acute upper respiratory tract disease in childhood.

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Childhood Upper Respiratory Tract Infections: To What Degree Is Incidence Affected by Day-Care Attendance?

David W. Fleming, MD, Stephen L. Cochi, MD, Allen W. Hightower, MS, and Claire V. Broome, MD

From the Meningitis and Special Pathogens Epidemiology Branch and Statistical Services Activity, Division of Bacterial Diseases, Centers for Disease Control, Atlanta

ABSTRACT. Risk factors for acute upper respiratory tract disease in childhood were evaluated in a population-based sample of the Atlanta metropolitan area. Mothers from 449 households containing 575 children less than 5 years of age were selected by random-digit dialing and questioned about upper respiratory tract infection and ear infection occurring in their children during the preceding 2 weeks. Household demographic and socioeconomic characteristics, maternal smoking history and child day-care attendance and breast-feeding information were also obtained. For children less than 5 years of age, the reported incidence of upper respiratory tract infection was 24%, and of ear infection, 6%. Controlling for the other variables measured, day-care attendance was associated with a significantly increased risk of both illnesses. For upper respiratory tract infection, increased risk was present for all children attending day care ($P = .02$, odds ratio = 1.6), whereas for ear infection, risk could be demonstrated only for full-time attendees ($P = .005$, odds ratio = 3.8). Maternal smoking was a second independent risk factor for a child's having upper respiratory tract infection (odds ratio = 1.7, $P = .01$). Thirty-one percent of all upper respiratory tract infection among day-care attendees and 66% of all ear infections among full-time day-care attendees were attributable to day-care attendance. Given the proportion of children in day care, 9% to 14% of the total burden of upper respiratory tract disease in this population was day care related. As use of child day-care facilities has increased, this specific exposure has become a major factor contributing to transmission of acute upper respiratory tract disease in childhood. *Pediatrics* 1987;79:55–60; *upper respiratory tract infection, day-care attendance.*

Infections of the upper respiratory system are the most common illnesses affecting children less than 5 years of age in the developed world. Although these illnesses, including acute upper respiratory tract infection and otitis media, may occasionally progress to more severe disease, most often they are self-limited. Despite their relatively benign nature, however, upper respiratory tract infectious illnesses are important causes of childhood morbidity, and their treatment consumes a substantial portion of available health care resources.[1]

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Reprint requests to (D.W.F.) Centers for Disease Control, Division of Bacterial Diseases, Atlanta, GA 30333.

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During the past decade, it has been demonstrated that risk of a number of childhood infections, including hepatitis,[2] diarrheal diseases,[3] and invasive *Haemophilus influenzae*,[4] is increased by day-care attendance. During this same time, the number of children younger than 5 years of age in the United States who are enrolled in day care has undergone a dramatic increase.[5] Although several studies have suggested that the risk of upper respiratory tract disease may be increased for some day-care attendees,[6-8] the importance of this association has not been well defined.

In this study, we examined risk factors for acquisition of infections of the upper respiratory system in children less than 5 years of age and specifically evaluated the role played by day-care attendance. Using population-based data, we determined the amount of illness attributable to this increasingly common childhood exposure.

METHODS

A cross section of all households containing children less than 5 years of age in Atlanta was surveyed by telephone from mid-July through mid-September 1984.

Sampling Procedure

Telephone numbers consisting of prefixes serving the study area and four randomly selected final

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digits were generated by computer. Every possible telephone number in the seven counties composing the metropolitan area (population 1.9 million) had an equal likelihood of being selected and called; no call-clustering techniques were used. Each number selected was called at least twice during business hours and at least six times during evenings and weekends before being discarded. Only households with children less than 5 years of age were enrolled.

Questionnaire Administration

Using a standardized questionnaire, trained interviewers obtained informed consent and then collected information from the guardian of the children in the household, preferably the mother. Data obtained included household demographic and socioeconomic characteristics, current maternal smoking history, and current breast-feeding and day-care attendance information for all children less than 5 years of age. All children within a given household were enrolled to ensure that our sample accurately represented all children in the study area with respect to household size and other related characteristics. A 15% sample of completed questionnaires was validated with a follow-up telephone call; no child's illness or day-care status was reclassified as a result of these calls.

Definitions

History of recent acute respiratory infection (cough, cold, or ear infection) was obtained directly from the child's guardian.[6,7,9] Because independent physician confirmation of illness was not required, we have used the term "ear infection" rather than otitis media to denote parental reported cases of infections of the ear. Criteria including antibiotic administration and physician visit were used if respondents needed clarification. We did not attempt to identify specific etiologic agents. Incidence of disease rather than duration of symptoms was assessed. To limit interviewer and respondent bias, illness history was elicited before parents were asked about day-care attendance. Children were considered case children if they had been ill with upper respiratory tract infection or ear infection at any time during the 2 weeks before the interview was conducted. Day care was defined as regular (>4 h/wk) supervised care of at least two unrelated children. Each child's day-care status was determined individually, based on enrollment at the time of interview. Part-time enrollment was defined as five to 39 hours' attendance per week and full-time as 40 or more hours per week.

Analysis

Two analyses of risk factors were undertaken, one for children reported to have upper respiratory tract infection and the other for children reported to have ear infection. An automatic interaction detection program was used to assist in selection of variables for inclusion in an unconditional logistic regression model. Only associations that were biologically plausible were considered. We did not attempt to analyze or control for transmission of illness within households because we could not distinguish between primary and secondary cases. The number of children younger than 5 years in the household, a variable included in the model, may serve as a surrogate for intrafamilial spread. Final models were obtained by first putting all candidate variables into the model and then eliminating any variable that was not significant and whose elimination did not alter the odds ratio estimates of significant variables by more than 15%. Etiologic fractions among exposed groups (EFe) were calculated by the formula: EFe = (probability of disease in exposed − probability of disease in unexposed)/(probability of disease in exposed) and were standardized for the entire population by weighting the values from individual strata according to the percentage of the population represented by that strata. The disease probabilities used were those determined by the regression model.

RESULTS

A total of 3,952 households in the study area were surveyed. Of these, 3,387 contained no children younger than 5 years, 78 were unwilling to answer whether children were present and 487 contained at least one young child. Of these latter households, complete interviews were obtained for 449 (92%). Twenty-six percent of households (118) contained more than one child, and information regarding illness was collected for 575 children.

Upper Respiratory Tract Infection

Twenty-four percent of the children surveyed (139/575) were reported to have had an upper respiratory tract infection during the 2 weeks before the interview. The incidence of reported illness was divided equally by sex with 24% of both boys (75/307) and girls (64/268) affected. Race did not appear to be a significant risk factor; illness was reported for 23% of white children (96/421), 27% of black children (40/146), and 40% of children of other races (4/10). The frequency of upper respiratory tract infection did vary somewhat with age; incidence in children younger than 36 months was 27% (91/338), and in children 36 months or older, 20% (47/232).

On univariate analysis, children who attended

day-care facilities appeared to be more likely than children who did not attend to have had symptoms of an upper respiratory tract infection during the 2 weeks preceding the interview (32% [55/175] of attendees *v* 21% [84/400] of nonattendees; $P = .01$, χ^2). A significant difference in risk between part-time and full-time attendance could not be demonstrated, although there was a suggestive trend in children younger than 36 months (42% [23/55] incidence in full-time attendees *v* 28% [11/39] in part-time attendees, $P = .2$, Fisher exact test). The type of day-care facility, ie, residential *v* nonresidential, and the length of time the child had been attending were not statistically associated with the likelihood of upper respiratory tract infection.

The association of day-care attendance with upper respiratory tract infection was further evaluated by logistic regression in a model that contained other variables considered to be possible risk factors for disease. These variables included family income, crowding (dichotomized at less than *v* equal to or more than one person per room), and number of children less than 5 years of age, maternal smoking, and child's race and age (dichotomized at 36 months). Current breast-feeding was included as a possible protective factor in children less than 6 months of age.

In this model, children who attended day care were significantly more likely than children who did not attend to have had a parent-reported upper respiratory tract infection during the 2 weeks before interview (odds ratio = 1.6, $P = .02$, Fig 1). In addition to day-care attendance, a second factor, maternal smoking, was also associated with increased risk of upper respiratory tract infection (odds ratio = 1.7, $P = .01$). The effects of day-care attendance and maternal smoking were independent of one another. Child's age, although itself not a risk factor (odds ratio = 1.2, $P = .4$), did significantly modify the effect of a third variable, household crowding. Living in crowded conditions was significantly associated with upper respiratory tract infection in children younger than 36 months (odds ratio = 2.4, $P = .02$) but not in children 36 months or older (odds ratio = 0.6, $P = .4$). No statistically significant association with risk of upper respiratory tract infection was seen for family income, number of children less than 5 years, and child's race, and no protective benefit of breast-feeding could be demonstrated (Table 1).

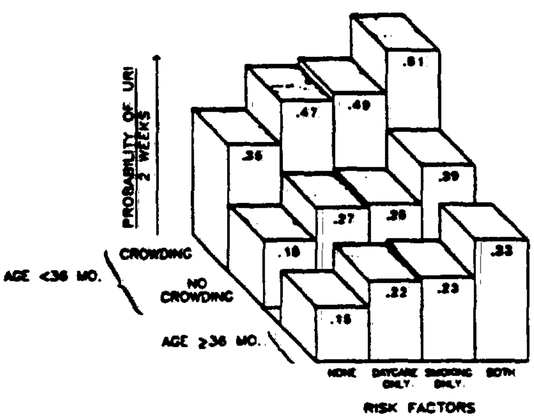

Fig 1. Probability of upper respiratory tract infection according to age, crowding, maternal smoking, and day-care status.

Clustering of illnesses within households did not seem to significantly affect the association of upper respiratory tract infection with day-care attendance. This relationship in households with only one child less than 5 years of age was similar to that in households with two ill children (odds ratio = 1.73 *v* 1.72), and the prevalence of day-care attendance in ill children from households containing no other children less than 5 years was similar to that observed in children from households with another ill sibling (41% [35/85] *v* 40% [12/30]).

Ear Infection

Six percent (34/575) of children less than 5 years of age were reported to have had an ear infection during the 2 weeks before the interview. Ear infection was reported more often for boys than girls (7.2% *v* 4.5%), but this difference was not statistically significant. Black children and white children were affected equally (6.1%); none of the ten children of other races were reported ill. Compared with upper respiratory tract infection, the incidence of ear infection was more influenced by age. Incidence was 8.6% (29/337) in children 0 to 35 months of age and 2.1% (5/233) in children 3 or 4 years of age. Children with ear infection were significantly more likely than children without ear infection to have had upper respiratory tract infection symptoms during the preceding 2 weeks (65% [22/34]) *v* 22% [116/535]; odds ratio = 6, $P < .001$, Fisher exact test).

Univariate analysis suggested that, as with upper respiratory tract infection, children attending day

TABLE 1. Variables Not Included in Final Upper Respiratory Tract Infection Model

Variable	Odds Ratio (Point Estimate)	P Value
No. of children <5 yr	0.7	.17
Race	1.1	.76
Breast-feeding	1.0	.98
Income ($)		
0–19,999	1.0	
10–34,999	1.5	.14
≥35,000	1.0	.91

care were at increased risk for development of ear infection. For ear infection, however, only children who attended a day-care facility 40 or more hours per week could be shown to be at increased risk. This association with full-time attendance was present when either all children or only children younger than 36 months were evaluated (Table 2). Although the number of children with ear infection who attended day-care full time was relatively small, the type of day-care facility, ie, residential *v* nonresidential, and the length of time the child had been attending did not appear to be associated with increased risk of disease.

The association between full-time day-care attendance and ear infection was evaluated in a logistic regression model containing the same variables that were used for the upper respiratory tract infection analysis. Concomitant upper respiratory tract infection was not considered as a separate risk factor because this illness may, in many instances, represent an intermediate step between exposure to a risk factor and ear infection.[8,10] Clustering of ear infections within a household occurred only once and, thus, was not a factor in analysis. In the ear infection model, full-time day-care attendance was strongly associated with increased risk of ear infection (odds ratio = 3.2, $P = .005$). Age was a second important predictor of disease, with children younger than 36 months at higher risk than children 36 months of age or older (odds ratio = 3.3, $P = .02$). Among young children, as with upper respiratory tract infection, crowding was an important factor predicting disease (odds ratio = 3.4, $P = .01$); in the older age group, data were insufficient to assess the effect of this variable (Fig 2). For ear infection, family income, number of children less than 5 years of age, maternal smoking, and child's race and breast-feeding status were not significantly associated with risk (Table 3). Two factors, maternal smoking and part-time day-care attendance, which were associated with the risk of upper respiratory tract infection, were not associated with the risk of ear infection. This finding may be due to the smaller numbers of children with ear infections and consequent lack of statistical power or alternatively to actual differences in risk factors for these two syndromes.

TABLE 2. Incidence of Ear Infection by Day-Care Attendance Status for All Children and Children 0 to 35 Months of Age

Day-Care Attendance Status	Incidence of Ear Infection (%)	
	All Children	0–35 Mo
Nonattendees	4.8 (19/395)	7.0 (17/244)
Part-time attendees	4.1 (3/73)	5.3 (2/38)
Full-time attendees	11.7 (12/102)	18.2 (10/55)
Status not available	(0/5)	(0/1)
Total	5.9 (34/575)	8.7 (29/338)

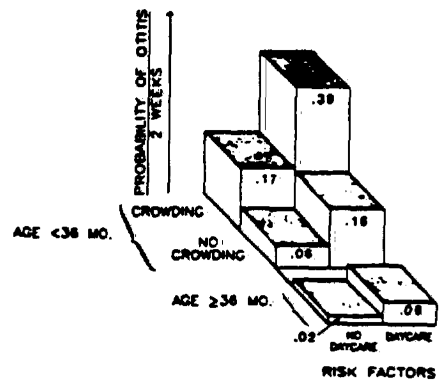

Fig 2. Probability of ear infection according to age, crowding, and day-care status.

TABLE 3. Variables Not Included in Final Ear Infection Model

Variable	Odds Ratio (Point Estimate)	P Value
No. of children <5 yr	0.7	.43
Maternal smoking	1.1	.82
Race	1.0	.93
Breast-feeding	1.9	.32
Income ($)		
0–19,999	1.0	
20–34,999	0.9	.87
≥35,000	0.8	.73

Attributable Risk

Perhaps the most meaningful measure of the amount of upper respiratory tract disease associated with day-care attendance is the etiologic fraction among the exposed children or $EFe_{(day\text{-}care)}$, which can be interpreted as the proportion of respiratory illness among children who attend day care that is directly related ("attributable") to this exposure.

In this study, the $EFe_{(day\text{-}care)}$ for upper respiratory tract infection, adjusted for the other variables shown to be associated with upper respiratory tract infection, was 31%. Thus, approximately one third of upper respiratory tract infections in children who attend day care may be attributable to this specific exposure. The $EFe_{(day\text{-}care)}$ for upper respiratory tract infections varied slightly by age and was 30% for children younger than 36 months and 33% for children 36 months of age or older.

For ear infections, the $EFe_{(full\text{-}time\ day\text{-}care)}$ was 66%, standardized for the other variables shown to be associated with ear infection, and thus approximately two thirds of ear infection contracted by full-time day-care attendees may be directly re-

TABLE 4. Etiologic Fraction Among Exposed Groups ($EFe_{(day-care)}$) and Population Attributable Risk of Upper Respiratory Tract Infection and Ear Infection Associated with Day-Care Attendance

Child's Infection and Age (Mo)	$EFe_{(day-care)}$	Children Attending Day-Care (%)	Population Attributable Risk (%)
Upper respiratory tract			
0–35	.30	29	9
≥36	.33	34	11
Ear infection			
0–35	.64	16	10
≥36	.68	20	14

lated to that specific exposure. The age-specific $EFe_{(full-time\ day-care)}$ for ear infection was 64% for children 0 to 35 months of age, those at highest risk, and 68% for children 3 and 4 years of age.

The amount of upper respiratory tract disease in all young children that is directly related to day-care attendance (the etiologic fraction among the population, also called the population attributable risk) depends not only on the proportion of illness related to attendance but also on the proportion of children who attend. This latter figure is likely to depend on a variety of factors including geographic region, season of the year, and age of the children involved. In Atlanta, during the summer of 1984, the population attributable risk for day-care attendance varied between 9% and 11% for upper respiratory tract infection and between 10% and 14% for ear infection, depending on child's age (Table 4).

DISCUSSION

Although more than 11 million children in the United States attend some form of day care,[11] estimates of risk have not been available for many of the illnesses to which these children are exposed, and the need for population-based studies has become increasingly apparent.[11,12] In particular, although the association between day-care attendance and infections of the upper respiratory system was suggested more than 35 years ago,[13] the contribution of day-care exposure to overall risk for these diseases has not been defined.

This study was designed to quantify the relation between day-care attendance and risk of childhood upper respiratory tract infections. Controlling for the effect of other risk factors, children in this cohort who were enrolled in day care were substantially more likely to have both upper respiratory tract infection and ear infection. Because these children were randomly selected from the general population, we could calculate that approximately one third of upper respiratory tract infections among day-care attendees and two thirds of ear infections among full-time day-care attendees were directly related to attendance. Because data regarding the proportion of children in the population attending day-care facilities were also available, we were able to estimate that 9% to 14% of all upper respiratory tract infections and ear infections in children less than 5 years of age may occur as a result of day-care attendance, a figure generalizable to other areas to the extent that day-care attendance patterns in Atlanta are similar to attendance patterns elsewhere. These estimates provide a useful assessment of the influence of day-care attendance on the overall risk of upper respiratory tract infection in young children. Respiratory illness results in an estimated 17.4 million physician visits a year in the United States[1] and for otitis media alone, an estimated annual expenditure of more than $2 billion.[14]

These percentages should be interpreted with appropriate caution. Having a child in day care may alter the likelihood that parents will notice and report illness in their children. This study determined a point estimate of risk based on parental reporting of illness during a 2-week period and, as such, should be viewed as only a first step in quantifying the effect of day-care attendance on the incidence of childhood upper respiratory tract infections. Nevertheless, the case definition based on parental reporting can be partially validated by the results of the analysis. If parents were reporting respiratory infections when no illness had occurred, one would not expect to find significant associations with crowding or maternal smoking. The substantial portion of upper respiratory tract infection linked to day-care attendance in this study suggests that it would be useful to determine whether specific etiologic agents may be particularly associated with this risk.

Additional studies that assess risk over season should be undertaken. For example, the risk of upper respiratory tract infection associated with day-care attendance calculated by this study may be a minimum estimate; day-care attendance may be more strongly linked with disease during the winter respiratory illness season when the likelihood of the introduction of upper respiratory tract infection into a day-care facility may be greater. Alternatively, a greater background incidence of viral infection during the winter might reduce the added risk associated with day-care attendance.

Several aspects of analysis other than the relation between upper respiratory tract illness and day-care attendance deserve comment. The similarity of the risk factor models for upper respiratory tract

infection and ear infection demonstrates the close association between these two illnesses and reaffirms the likely role of upper respiratory tract infections in the pathogenesis of ear infection.[8,10] The data regarding maternal smoking underscore the link between passive exposure to smoke and development of upper respiratory tract infection in children.[15,16] In this study, the proportion of upper respiratory tract infections in children of smoking mothers attributable to this exposure (34%) and the total population attributable risk (10%) were comparable to those calculated for day-care attendance.

As risk factors, however, there is a major difference between maternal smoking and day-care attendance. Whereas maternal smoking is totally preventable, day-care attendance is not. This difference highlights an increasingly obvious dilemma: child day care provides an irreplaceable service; yet, by its nature, it also results in enhanced transmission of infectious illnesses. The most practical approach to this problem—reduction of risk among those children who attend—rests on the assumption that differences in day-care facilities and children's exposures within those facilities may affect degree of risk. For diarrheal disease, this assumption seems warranted; risk has been shown to be influenced by a variety of specific day-care characteristics.[3] Whether the same is true for respiratory disease remains an open question. Identification of specific factors that are associated with increased risk of upper respiratory tract disease within day-care facilities should be a primary goal of future study.

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Kallail, K.J., Rainbolt, H.R., Bruntzel, M.D. "Passive Smoking And Middle Ear Problems In Kansas Public School Children" J Commun Disord 20: 187-196, 1987.

This study was conducted by investigators who were interested in determining whether parental smoking influenced the incidence of middle ear problems in children. Children in the Kansas school system identified as having middle ear problems were compared with children who passed their school's hearing test. The researchers report that the investigation revealed that there were no differences between the two groups of children for the presence of smoking, the amount and type of smoking, and the number of smokers in the home. Therefore, they concluded that "exposure to cigarette smoke in the home apparently was not a risk factor for middle ear problems in children.

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PASSIVE SMOKING AND MIDDLE EAR PROBLEMS IN KANSAS PUBLIC SCHOOL CHILDREN

KEN J. KAI LAIL
University of Kansas School of Medicine—Wichita

HARRY R. RAINBOLT
Kansas State University

MELVIN D. BRUNTZEL
Kansas Department of Education

Survey data from parents of Kansas school children identified as having middle ear problems were compared to data obtained from parents of children who passed their school's hearing screening tests. The results of the investigation revealed that there were no differences between the two groups of children for the presence of smoking, the amount and type of smoking, and the number of smokers in the home. Exposure to cigarette smoke in the home apparently was not a risk factor for middle ear problems in children.

INTRODUCTION

Research over the past half-century indicated that smoking causes cancer of the lung, larynx, oral cavity, and esophagus, and is significantly associated with pancreas, urinary bladder, and kidney cancer in both men and women (U.S. Department of Health and Human Services (DHHS), 1981). Further, a clear dose–response relationship has been established between smoking and a number of disease states.

Public awareness of the dangers of smoking has steadily increased over the years, including the danger of "passive" or involuntary smoking (DHHS, 1981). Several investigators have reported the negative effect of parental smoking on children's health (Bergman and Wiesner, 1976; Cameron et al., 1969; Cameron and Robertson, 1973; Colley, 1974; Colley et al., 1974; Comstock et al., 1971; Harlap and Davies, 1974; Kraemer et al., 1983; Saxton, 1978; Tager et al., 1979). One of the most frequently mentioned group of illnesses in children that has been associated with parental smoking was respiratory illnesses.

Address correspondence to Ken. J. Kallail, Ph.D., UKSM—W Dept. of Family and Community Medicine 1010 N. Kansas Wichita, KS 67214.

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The relationship of smoking and hearing abilities also has been investigated. Zelman (1973) found that smokers manifested greater hearing losses than nonsmokers, especially at the higher frequencies. Smokers also have been shown to have less temporary threshold shifts than nonsmokers (Dengerink et al., 1984). Cantrell (1970) reported that tobacco smoking caused eustachian tube malfunction and adversely affected the tympanic membrane. Marston, Sterrett, and McLennan (1980), however, found no significant effect on the admittance characteristics at the plane of the tympanic membrane in young adult smokers.

With regard to passive smoking and hearing ability in children, Saxton (1978) reported that infants whose mothers smoked during pregnancy manifested reduced or impaired auditory function as compared to infants whose mothers did not smoke. In addition, Kraemer and colleagues (1983) found that exposure to two or more household cigarette smokers increased children's risk for persistent middle ear effusions (PMEE) nearly threefold-fourfold with exposure to smoke from more than three packs per day. Children with the combined factors of atopy, nasal congestion, and exposure to cigarette smoke were six times more likely to manifest PMEE.

Examination of the literature indicated a paucity of data regarding the effects of passive smoking on the incidence of middle ear problems in children. In a reanalysis of some of the Kraemer et al. data, Rogers and colleagues (1984) suggested that there was not enough evidence to establish cigarette smoke exposure as a risk factor for PMEE. Further data, therefore, need to be obtained to determine the effects of passive cigarette smoking in children and middle ear problems. Also, because the Kraemer et al. data were obtained in Seattle, a city that has reduced air quality, similar information from a relatively "clean" air environment, such as Kansas (National Commission of Air Quality, 1981), should provide useful, additional data.

The purpose of the present investigation was to obtain survey data from parents of Kansas school children identified as having middle ear problems and compare them to data obtained from parents of children who passed their school's hearing screening tests. Information was obtained regarding the number of household smokers, the amount and type of household smoking, and the number of middle ear problems.

PROCEDURES

A questionnaire (see Appendix A) was developed to obtain the pertinent data from parents of Kansas school children. The questionnaire was attached to a cover letter for the parent (or guardian) of each child, which provided general information about the investigation and the rights of the participants.

The questionnaires were copied on different colored paper for easy identification. White forms were given to parents of children who had

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been identified by a physician as having a middle ear problem. These children had failed the school's hearing screening procedures and were referred to a physician for diagnosis. Blue forms were given to parents of children who had passed the school's hearing screening test.

The exact hearing screening procedures might have varied slightly between school districts. The minimum procedures established by state regulations are bilateral pure tone screening at 25 dB HL for the frequencies .5, 1, 2, 4, and 6 kHz (Kansas Department of Education (DOE)/Department of Health and Environment (DHE), 1980). Each child who passed the screening test responded appropriately to the test stimuli. Each child who failed the screening test was rescreened at a later date. If the child failed the rescreening, a pure-tone threshold was obtained. A child was referred for a complete audiometric evaluation and an examination by a physician if the hearing test results showed a loss of 30 dB at two frequencies or 35 dB at one frequency in either ear (KDOE/DHE, 1980). Personnel in some school districts with the appropriate equipment obtained tympanograms as well. The experimental (i.e., diagnosed by a physician with middle ear problems) and control (i.e., passed school's hearing screening) groups, therefore, did not undergo identical subject selection procedures. The subject selection procedures, however, followed the procedures for the identification of middle ear problems in Kansas public schools. The authors determined that these procedures were appropriate for the present survey investigation.

A total of 1600 questionnaires, 800 white forms and 800 blue forms, were divided between the special education directors of each school district in Kansas by the Kansas Department of Education. Ten questionnaires of each color were given to smaller districts; 25 questionnaires of each color were given to larger districts. The directors had been informed, in advance, of the investigation.

Written instructions were provided with the questionnaires to each director. The instructions included:

1. the meaning of the color code;
2. the number of questionnaires provided;
3. the procedures used to code subjects, sex, school district, and age;
4. the procedures to match children from the experimental (i.e., diagnosed with middle ear problems) and control (i.e., passed school's hearing screening test) groups; and,
5. the deadline date and address to return the questionnaires.

Subjects were matched by age, within ± 6 months, and sex. For the statistical analyses, the subjects were grouped by age according to the following categories: less than or equal to 6;6, 6;6 to 8;0, and greater than 8;0 (years;months). Each matched-subjects pair fell within the same age category; no matched pairs crossed age categories. All subjects were se-

lected, according to the hearing screening and medical exam results, by the staff of the local school district.

RESULTS

A total of 344 questionnaires (21.5%) were returned to the investigators. Of those returned, a total of 238 questionnaires (119 matched pairs) were used in the analyses. One hundred and six questionnaires were excluded from study for a variety of reasons, most often because they lacked an appropriately matched sample. Table 1 shows a breakdown of the 238 subjects by age and sex.

The results of the investigation revealed a significant difference between the two groups for the number of middle ear problems during the last year ($\chi^2 = 96.6$; $df = 3$; $p < .0001$). The members of the experimental group, each of whom was identified by a physician as manifesting a middle ear problem, had significantly more episodes of middle ear problems than the members of the control group, each of whom passed the school's hearing screening test. This finding was important because it was conceivable that some children with a middle ear problem might pass a pure-tone screening, thereby confounding the control group.

There were nonsignificant differences between the two groups on items regarding the presence of smoking in the home ($\chi^2 = 2.84$; $df = 1$; $p > .05$), the number of smokers in the home ($\chi^2 = 2.88$; $df = 2$; $p > .05$), the type of smoking in the home ($\chi^2 = 3.52$; $df = 2$; $p > .05$), and the amount of cigarette ($\chi^2 = 6.55$; $df = 4$; $p > .05$), cigar ($\chi^2 = 0$; $df = 1$; $p > .05$), and pipe ($\chi^2 = 3.23$; $df = 1$; $p > .05$) smoking in the home.

Figure 1 shows the number of homes in each group with the presence and absence of smoking. Cigarette smoking was by far the greatest type of smoking in the home. One hundred and seven respondents indicated that cigarette smoking occurred in the home as compared to 12 respondents who indicated that some other type of smoking occurred.

Figure 2 shows the number of household smokers for each group. Kraemer and colleagues (1983) reported a greater risk for PMEE in children with exposure to two or more household smokers or smoke from more

Table 1. A Breakdown by Age and Sex of the 238 Subjects

		Age group		
Sex	< 6;6	6;6–8;0	> 8;0	Total
M	38	36	60	134
F	30	48	26	104
Total:	68	84	86	238

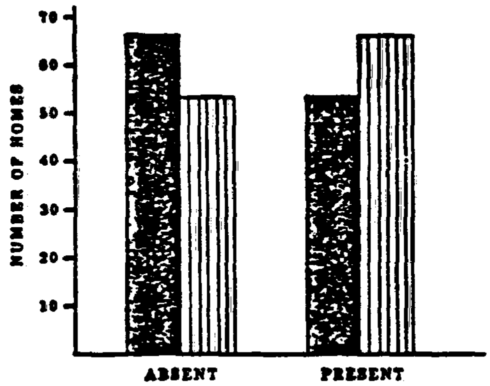
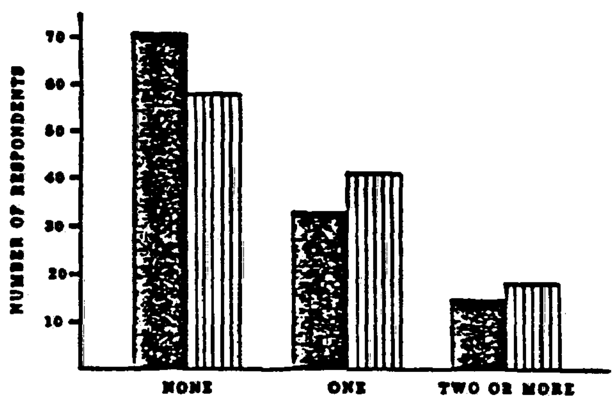


Figure 1. The number of homes with smoking absent and present in the control (solid black) and experimental (black lines) groups.

than three packs of cigarettes per day. A nonsignificant trend is shown in Figure 2 in which the experimental group exhibited more homes with more smokers than the control group. For example, 19 respondents in the experimental group and 15 respondents in the control group reported two or more smokers in the home.

Figure 2. The number of respondents in the control (solid black) and experimental (black lines) groups by the number of household smokers.



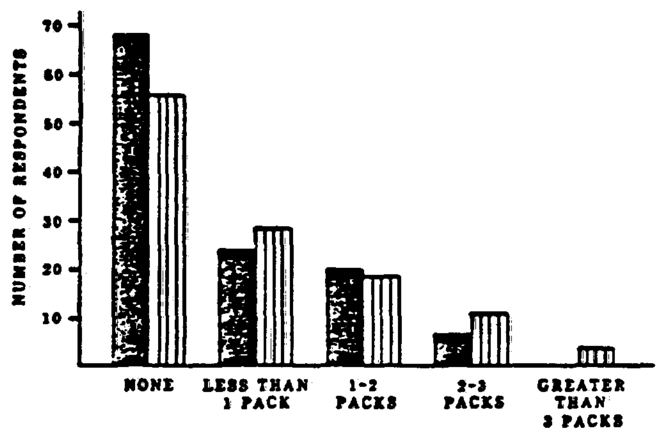


Figure 3. The number of respondents in the control (solid black) and experimental (black lines) groups by the amount of cigarette smoking in the home.

Figure 3 shows the number of respondents in each group by the amount of cigarette smoking in the home. A nonsignificant trend is shown in Figure 3 in which the experimental group reported more smoke in the home than the control group. For example, four respondents in the experimental group and none in the control group reported smoke from more than three cigarette packs per day in the home.

These nonsignificant trends also appeared for cigar and pipe smoking. A greater amount of cigar and pipe smoking was reported for the experimental group. Two respondents in the experimental group and one in the control group reported that cigars were smoked in the home for more than three hours per day. Three respondents in the experimental group and none in the control group reported that pipes were smoked in the home for more than one hour per day.

The results also showed no significant differences in the episodes of middle ear problems by age ($\chi^2 = 8.51$; $df = 6$; $p > .05$) or by sex ($\chi^2 = .41$; $df = 3$; $p > .05$). Apparently, the matching procedures used in this investigation were adequate.

DISCUSSION

Survey investigations traditionally have low response rates. Unfortunately, low response rates may render the results of a survey questionable. The need for follow-up to nonrespondents has been emphasized earlier,

(Ferber et al., 1980). In the present investigation, the low response rate seemed to result from the failure of the school personnel to distribute and collect the surveys by the established deadline rather than a reluctance of parents to respond. The most common reasons for failing to return the completed questionnaires were that the school personnel forgot to distribute them and that they were too busy with end-of-year responsibilities.

Certainly, if some parents (e.g., smokers) were more likely not to respond than others (e.g., nonsmokers), the survey results would be invalid. The fact that there were nonsignificant differences for the number of smokers in the matched pairs for each group seemed to validate the results. Apparently, smokers and nonsmokers were equally likely to complete the survey.

The results of the present investigation revealed no differences between the experimental and control groups for the presence of smoking, the amount and type of smoking, and the number of smokers in the home. It also was interesting to note a nonsignificant trend for children exposed to very heavy smoking in the home often to have middle ear problems. For these children, a larger sample might have revealed significant differences. Further study of this important health factor is encouraged.

The present study supported the conclusions of Rogers et al. (1984) that exposure to cigarette smoke in the home was not a risk factor for middle ear problems in children. Rogers et al. (1984) reanalyzed previous data from Kraemer et al. (1983) by controlling for the influence of nasal congestion. They suggested that it was the nasal congestion that influenced Kraemer's significant results, not exposure to household cigarette smoking.

Another factor to be considered in the relationship between passive smoking and middle ear problems in children is the effects of air quality. A large body of evidence has indicated a qualitative relationship between air pollution and disease (Perera and Ahmed, 1979). As mentioned earlier, the Seattle, Washington area (where Kraemer's data were collected) has reduced air quality. The state of Kansas has a relatively "clean" air environment. Cigarette smoking and air pollution have been recognized by epidemiological experts as independent factors, which when combined produce an additive and in some cases a synergistic effect (Perera and Ahmed, 1979). The relative elimination of air pollution in the present investigation suggested that tobacco smoke exposure alone might not be as great a risk factor for middle ear problems in children as previously assumed.

It should be pointed out once again that the health risks of smoking, both active and passive, were evident in the literature. The relationship between passive smoking and middle ear problems in children, however, is apparently a complex one. The risks of middle ear problems from exposure to tobacco smoke most probably increase when in combination

with other risk factors, such as air pollution or nasal congestion, or when the smoke exposure is excessively heavy.

The authors acknowledge the personnel from the many school districts who participated in the investigation. Also, the authors thank Dr. George Milliken, Department of Statistics, at Kansas State University for his assistance in the statistical analyses.

APPENDIX A: QUESTIONNAIRE

I.D. # ___ ___ ___ ___ Age ___

District/Cooperative # ________

Please respond to the following items completely and accurately.

1. For the school-age child identified above, what is the number of episodes of middle ear problems during the last year?
   ___ None ___ 1 to 2 ___ 3 to 6 ___ more than 6
2. What was the most recent method of treatment for the middle ear problem?
   ___ None ___ Medication ___ Surgery
   ___ antihistamine ___ PE tubes (tubes placed in eardrum)
   ___ antibiotic ___ mastoidectomy
   ___ antihistamine and antibiotic ___ other (specify)
   ___ other (specify)
3. How has the number of episodes of middle ear problems changed over the last three years?
   ___ No change ___ Increased ___ Decreased
4. Does smoking of any kind occur in your place of residence?
   ___ Yes ___ No
   If "yes", please complete the remainder of the form.
5. Check each type of smoking that occurs in the place of residence on a typical day (consider both residents and visitors).
   ___ Cigarette ___ Cigar ___ Pipe
6. Check the number of smokers living in your place of residence.
   ___ 1 ___ 2 ___ 3 or more
7. Check the total amount of cigarette smoking by all smokers that occurs within your place of residence on a typical day.
   ___ None ___ Less than one pack
   ___ At least one pack but less than two
   ___ At least two packs but less than three
   ___ Three packs or more
8. Check the total amount of pipe smoking by all smokers that occurs within your place of residence on a typical day (double count if two people smoke a pipe at the same time).
   ___ None ___ Less than one hour
   ___ At least one hour but less than three hours
   ___ At least three hours but less than five hours
   ___ Five hours or more
9. Check the total amount of cigar smoking by all smokers that occurs within your place of residence on a typical day (double count if two people smoke cigars at the same time).

____ None ____ Less than one hour
____ At least one hour but less than three hours
____ At least three hours but less than five hours
____ Five hours or more

10. Please add any comments that you feel may be helpful to our investigation. If necessary use the back of this page.

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2024228205

Tainio, V.M., Savilahti, E., Salmenpera, L, Arjomaa, P, Siimes, M.A., Perheentupa, J. "Risk Factors for Infantile Recurrent Otitis Media: Atopy but Not Type of Feeding" Pediatr Res 23: 509-512, 1988.

ABSTRACT. We followed 183 infants from birth to 2.3 yr of age. Of these infants 28 had recurrent otitis media (ROM), defined as five or more separate episodes of otitis media (OM) during the first 2 yr of life or four such episodes during their 2nd yr. The OM presented during their 1st yr (early onset ROM) in 12 infants and during their 2nd yr (2nd yr ROM) in 16. Eighty infants had no OM and served as a comparison group. Regarding type of feeding, the infants with early-onset ROM did not differ from their age-matched pairs in the comparison group either one month before the first OM or at the time of first episode of OM. Exclusive breast-feeding did not prevent OM and early weaning was not a risk factor for ROM. Atopy was associated with ROM with a relative risk of 1.9 (95% confidence limits 1.2-3.2). It was particularly prevalent among the infants with early-onset ROM, in 67 versus in 25% in the comparison group ($p < 0.01$). During the 2nd yr daily contact with five or more children was associated with ROM with a relative risk of 2.1 (1.3-3.3). The infants with 2nd-yr ROM were in daily contact with more children than the comparison group (mean 11 versus 5; $p < 0.001$). Parental smoking was more frequent among the infants with ROM than in the comparison group (54 versus 33%; $p < 0.05$). In the infants with early-onset ROM plasma concentration of IgM antibodies to cow's milk was highest at the age of 9 months, and the concentration of IgE was highest at the ages of 9 and 12 months. In conclusion atopy, not the type of feeding, is a risk factor for early-onset ROM, and daycare outside the home for ROM during the 2nd yr.

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PEDIATRIC RESEARCH

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Risk Factors for Infantile Recurrent Otitis Media: Atopy but Not Type of Feeding

V-M. TAINIO, E. SAVILAHTI, L. SALMENPERÄ, P. ARJOMAA, M. A. SIIMES, AND J. PERHEENTUPA

Children's Hospital, University of Helsinki, Helsinki, Finland

ABSTRACT. We followed 183 infants from birth to 2.3 yr of age. Of these infants 28 had recurrent otitis media (ROM), defined as five or more separate episodes of otitis media (OM) during the first 2 yr of life or four such episodes during their 2nd yr. The OM presented during their 1st yr (early-onset ROM) in 12 infants and during their 2nd yr (2nd yr ROM) in 16. Eighty infants had no OM and served as a comparison group. Regarding type of feeding, the infants with early-onset ROM did not differ from their age-matched pairs in the comparison group either 1 month before the first OM or at the time of first episode of OM. Exclusive breast-feeding did not prevent OM and early weaning was not a risk factor for ROM. Atopy was associated with ROM with a relative risk of 1.9 (95% confidence limits 1.2–3.2). It was particularly prevalent among the infants with early-onset ROM, in 67 *versus* in 25% in the comparison group ($p < 0.01$). During the 2nd yr daily contact with five or more children was associated with ROM with a relative risk of 2.1 (1.3–3.3). The infants with 2nd-yr ROM were in daily contact with more children than the comparison group (mean 11 *versus* 5; $p < 0.001$). Parental smoking was more frequent among the infants with ROM than in the comparison group (54 *versus* 33%; $p < 0.05$). In the infants with early-onset ROM plasma concentration of IgM antibodies to cow's milk was highest at the age of 9 months, and the concentration of IgE was highest at the ages of 9 and 12 months. In conclusion atopy, not the type of feeding, is a risk factor for early-onset ROM, and daycare outside the home for ROM during the 2nd yr. (*Pediatr Res* 23: 509–512, 1988)

Abbreviations

OM, otitis media
ROM, recurrent otitis media
CM, cow's milk
CMA, cow's milk allergy

OM may occur in early infancy, but its incidence increases rapidly after the age of 6 months (1, 2). In a Finnish follow-up study 5% of infants had OM during the first 6 months of life, 36% during their 1st yr, and 59% during their 2nd and 3rd yr (3). Several risk factors have been identified: daycare outside the home (4), enlarged adenoids (5), feeding in the horizontal position (6), smoking at home (7), and atopy (8, 9), particularly food allergy (9). Some studies suggest a protective effect of breast-feeding (3, 10, 11) but others detect none (2, 13). Any study of the impact of feeding on morbidity is beset with numerous methodologic limitations (14).

In this prospective study we followed 198 infants throughout the 1st yr of life, carefully recording their feeding regimen, illnesses, and environment. For 183 of the infants similar data were obtained from the parents regarding the 2nd yr by a detailed questionnaire. From these data we analyzed the risk factors for ROM.

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Correspondence, V-M Tainio, Children's Hospital, University of Helsinki, 00290 Helsinki, Finland.
Supported by grants from the Sigrid Juselius Foundation, the Foundation for Pediatric Research and the Foundation for Nutrition Research, Helsinki, Finland.

MATERIALS AND METHODS

We followed 198 healthy newborns from birth; they were seen at clinic visits at 2, 4, 6, 9, and 12 months of age, and whenever they had any problems regarding feeding, nursing, or illness. At a mean age of 2.3 yr 60 of the infants were examined by one of us (V-M.T.), and a questionnaire was sent to each family. The questionnaire was returned by 183 families. Data concerning health, feeding, and socioenvironmental factors were recorded at each visit and from the questionnaire (15–17). All medical care during the 1st year was provided by one pediatrician (L.S.). The illnesses during the 2nd yr were treated by physicians chosen by the parents. The services of health center physicians are free of charge. General health insurance covers part of the fees of private practioners, and additional voluntary insurance usually covers such fees completely. Therefore parents seek medical care for their infants very readily, and pediatric and otologic services are commonly used. A venous blood sample was taken at each clinic visit, and levels of plasma IgE and cows' milk antibodies were measured (15–17). The plasma levels of IgG and IgM CM antibodies are expressed as percentages of a standard plasma with a high level of CM antibodies.

OM was defined as an otoscopic loss of translucency and landmarks, clear inflammation or bulging of, lack of mobility of, or purulent discharge from the tympanic membrane. Infants with OM or ROM were symptomatic.

ROM was defined as the number of separate episodes of OM occurring in the 90th percentile of the whole series of infants during the first 2 yr (five episodes), or in the 95th percentile during the 2nd yr (four episodes). An OM occurring 2 months after a previous OM and after a normal otoscopic finding during the interval was regarded as a separate episode. Early-onset ROM was ROM with the first OM during the 1st yr, and 2nd-yr ROM was ROM with first OM during the 2nd yr.

Atopy. The diagnosis was based on the presence of pruritic dry dermatitis, urticarial eruption, three or more episodes of wheezy bronchitis, or three of the following: rhinorrhea lasting more than 1 month, frequent itching and/or watering of the eyes, two episodes of wheezy bronchitis, gastrointestinal symptoms provoked by foods (16). The most frequent problems were cutaneous.

CMA was diagnosed if skin, respiratory, or gastrointestinal signs developed repeatedly after ingestion of cow's milk and

disappeared on a cow's milk-free diet, and were provoked by a cow's milk challenge test at hospital.

Feeding. All mothers were encouraged to breast-feed as long as possible. Of the 198 infants, 32 were completely weaned by 3.5 months of age. At 6 months of age 101 and at 9 months 31 infants were still exclusively breast-fed, having no milk formula or other complementary food. The weaned infants followed a standard dietary program including an adapted formula (Tutteli, Valio, Ltd Helsinki: protein concentration 16 g/liter), fruit and vegetables from 3 months of age, and cereals and meat from 5 months. Pasteurized whole cow's milk was substituted for the formula from 9 months. For 98 infants, the most frequent food allergens (eggs, fish, tomatoes, citrus fruit, chocolate, peas, and strawberries) were excluded from the diet until 12 months of age, on the advice given by well baby clinics to the families with a history of atopy.

Socioeconomic background. Of the mothers, 23% had an academic background and another 39% had some other form of higher education; 65% were employed until shortly before the infant's birth, and 38–59% were employed during the follow-up after a maternity leave of 10 months. By self-assessment the economic status was good in 28% of the families, satisfactory in 64%, and unsatisfactory in 8%. The mean housing space was 16 ± 7 (SD) m^2/person. There were three single mothers. In 42% of the families the infant was the only child, 22% of families had two children, and 36% three or more children.

Smoking habits and pets. Of the mothers 15% and of the fathers 32% were smokers, and in 36% of the families either one or both smoked. Smoking took place mainly outside the home. Smoking is forbidden in daycare family homes and daycare centers. A pet was present in 20% of the homes.

Daycare and contact with other children. At 12 months of age 62% of the infants were cared for at home by their own mother, 18% in another family-type arrangement, and 20% at a public daycare center. At 24 months the respective numbers were 41, 29, and 24%; 6% had another arrangement. The median number of children in home care was two, in the family-type setting four, and at a daycare center 12.

Statistical analyses. The χ^2, t tests, and multivariate analysis of variance were used for comparisons. Because of skewness of distributions of plasma IgE and cow's milk antibodies, values were analyzed after log transformation. Predictive factors for ROM and for more than one, two, three, four, or five episodes of OM were searched for by stepwise logistic regression. Seventeen variables were tested. The variables were treated as categorical. Some variables were categorical by nature (variables 6, 7, 8, 16, and 17) and others were divided into two categories either in a way that was relevant for the study (i.e., daycare at home or outside the home) or by choosing a cutoff point using the distribution of the whole series of 183 infants (Table 1).

Table 1. *Risk factors for infantile ROM**

	Relative risk ± (95% confidence limit)
1. High no. of upper respiratory tract infections (≥5 during the first 2 yr of life)†	
2. Short duration of exclusive breast-feeding (≤74 days)†	
3. Early regular formula feeding (before the age of 99 days)†	
4. Early complete weaning from breast (before the age of 99 days)†	
5. Early introduction of solid foods (before the age of 131 days)†	
6. Positive family history for atopy	
7. Occurrence of own atopic disease	1.9 (1.2–3.2)
8. Occurrence of CMA	
9. Low educational level of mother: (no higher education)	
10. Low occupational class of mother: (no regular work)	
11. Low social class of family: (lowest of 3 classes)	
12. Small size of home (≤45 m^2)†	
13. Daycare outside the home at the age of 12.0 mo	1.9 (1.1–3.2)
14. High no. of child contacts (≥5 during yr 2)	2.1 (1.3–3.3)
15. Sleeping arrangements (with siblings or parents)	
16. Smoking of parents (one or both)	
17. Pet at home	

* Relative risk is given only where significantly > 1.0. ROM was defined as ≥5 episodes of OM during the first 2 yr or ≥4 episodes during the 2nd yr.

† This limit separates one quartile of the study group.

RESULTS

OM. For the study of ROM, the following groups were distinguished among the series of 183 infants: ROM 28 infants, early-onset ROM 12 infants, 2nd-yr ROM 16 infants, and a comparison group of 80 infants who had no OM during their first 2 yr. In addition 151 infants had no OM during their 1st year and 96 during their 2nd yr. In 14 of the 28 infants with ROM adenoidectomy was done and nine had typanostomy tubes placed. Of the total number of otorhinologic operations in the series, 70% were in infants with ROM.

Upper respiratory tract infections. The frequency of upper respiratory tract infections was not a risk factor for ROM (Table 1). However, during the 1st yr such illnesses were more frequent in the infants with ROM than in the comparison group (6.0 ± 0.6 *versus* 4.0 ± 0.2 infections, $p < 0.01$). There was no such difference during the 2nd yr (2.8 ± 0.3 *versus* 3.4 ± 0.5, respectively).

Feeding. None of the feeding variables tested were risk factors for ROM (Table 1) or for OM (Table 2). The infants with early-onset or 2nd-yr ROM did not differ from the comparison group in this respect (Tables 3 and 4). The 34 infants with one or more episodes of OM during the 1st yr of life were compared with matched pairs from the comparison group (matched for age, season of birth, smoking of parents, type of daycare, and own atopy) 1 month before the first OM and at the time of first episode of OM. There were altogether three more pairs in whom at the time of the first episode of OM, the infant with OM was weaned more fully than the comparison infant. The infants with early-onset ROM were compared with their matched pairs. Altogether there were no statistical significant differences in these comparisons. Ongoing breast-feeding did not prevent OM; six of the 12 infants with early-onset ROM had the first OM when still exclusively breast-fed and two others when partially breast-fed.

Atopy appeared in 14 infants during the 1st yr and in another 31 during the 2nd yr. It was associated with a 1.9-fold relative risk of ROM (Table 1) and was more common among the infants with ROM than in the comparison group (50 *versus* 25%, $p < 0.01$). The prevalence of atopy was higher among infants with early-onset ROM than in those with 2nd-yr ROM (67 *versus* 38%, $p < 0.05$). The infants with early-onset ROM had the highest concentration of plasma IgE at 9 and 12 months of age (Table 5).

CMA was not a risk factor for ROM (Table 1). Seven infants had cutaneous CMA during the 1st yr. They tended to have OM more frequently during the 1st yr than the others (1.5 ± 0.6 *versus* 0.4 ± 0.1; $p < 0.1$). Only two of these seven infants had no OM during the 1st year *versus* 145 of the other 186 infants ($p < 0.001$). However, only one of the seven infants with CMA had ROM.

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Table 2. *Relative risks (and their 95% confidence limits) of OM and its recurrence**

No. of episodes of OM	≥1 (n = 76)	≥2 (n = 55)	≥3 (n = 38)	≥4 (n = 26)	≥5 (n = 17)	ROM (n = 28)
Day care outside the home at age of 12.0 mo	1.7 (1.2–2.3)	1.6 (1.1–2.3)	1.9 (1.3–3.0)	1.8 (1.1–3.0)	1.7 (1.0–2.8)	1.9 (1.1–3.2)
High number of child contacts (>5 during yr 2)		1.4 (0.9–2.0)		1.8 (1.1–2.9)	2.7 (1.5–5.2)	2.1 (1.3–3.3)
Occurrence of own atopic disease					2.2 (1.2–4.2)	1.9 (1.2–3.2)
Smoking of parents (one or both)			1.7 (1.1–2.7)			

* Relative risk is given only where significantly > 1.0. The other 13 variables in Table 1 were not significant risk factors for OM or its recurrence.

Table 3. *Feeding parameters in infants with ROM and in the infants without OM: median and 1st and 3rd quartiles are given for age in days**

	Infants with early-onset ROM (n = 12)	Infants with 2nd-yr ROM (n = 16)	Infants without OM (n = 80)
First exposure to cow's milk	242 (78–258)	98 (36–281)	240 (82–291)
Start of regular formula feeding	242 (180–278)	258 (80–290)	251 (111–294)
Complete weaning from breast	335 (186–404)	238 (98–347)	286 (111–354)
Introduction of solid foods	185 (133–233)	176 (132–239)	190 (134–235)

* There were no statistically significant differences between these groups, or between all infants with and those without ROM.

Table 4. *Prevalence of exclusive breast-feeding among infants with ROM and infants without OM**

Age (mo)	Infants with early-onset ROM (n = 12) (%)	Infants with 2nd-yr ROM (n = 16) (%)	Infants without OM (n = 80) (%)
2	92	75	81
6	58	50	60
9	0	31	18

* There were no statistically significant differences between these groups or even between all infants with and without ROM.

Cow's milk antibodies. The mean levels of IgG cow's milk antibodies were similar in the ROM group and the comparison group. At 12 months of age a higher proportion of infants with ROM than of the comparison group (22 *versus* 6%, $p < 0.05$) had supranormal (>2.0 SD) levels of IgG cow's milk antibodies. At 9 months of age the infants with early-onset ROM had a higher mean level of IgM cow's milk antibodies than the infants with 2nd-yr ROM (58 *versus* 12%, of the standard plasma, $p < 0.05$).

Socioeconomic background. The group with ROM did not differ from the comparison group in the educational level of the mother or the economic status of the family. The mean absolute and relative size of the home was similar, as was the mean size of the family.

Number of child contacts and day-care. The number of daily child contacts during the 2nd yr was a predictive factor for ROM. The relative risk was 2.1 (Table 1) if the number of child contacts was five or more. During their 2nd yr the infants with 2nd-yr ROM had daily contacts with a mean of 11 *versus* five children for the infants with early-onset ROM and five for the comparison group ($p < 0.001$). Daycare outside the home at the age of 1.0 yr was also a risk factor for ROM (Table 1), even for the first episode of OM (Table 2). The proportion of infants having daycare outside the home during both their 1st and 2nd yr was higher among the infants with ROM than among those of the comparison group (59 and 69% *versus* 24 and 44%; $p < 0.05$). The same was true for those attending a daycare center during their 2nd year (44 *versus* 18%, $p < 0.05$). However, 10 of the 12 infants with early-onset OM had the first OM when still being taken care of at home. Ten of 16 infants with 2nd-yr ROM had daycare outside the home when OM presented.

Smoking and pets. Of the parents, 55% smoked in the ROM group *versus* 33% in the comparison group ($p < 0.05$). There was no such significant difference between the groups in the proportion of homes with a pet (16 *versus* 20%).

DISCUSSION

We noticed a rapid increase in the incidence of OM from 22% during the infants' 1st yr to 48% during their 2nd yr. The incidence of OM is highest during the first 2 yr of life (1–2, 18). Our values were close to those reported (2, 3, 18). There are no accepted criteria for ROM; our definition (five or more episodes during the first 2 yr or four or more during the 2nd yr) resulted in an incidence of 15%. A similar incidence (13%) was found in another Finnish study (3), but much higher values (30%) have been reported (1, 2).

We found different risk factors in infants with early-onset and 2nd-yr ROM. Most of the infants with early-onset ROM had atopy and the mean plasma level of IgE was higher in these infants than in the infants with 2nd yr ROM and those without OM. This association with atopy has been noted earlier in regard to secretory OM (19, 20), but has recently been disputed (3, 21). The majority of infants with early-onset ROM were partially or exclusively breast-fed, were cared for at home, and had a small number of daily child contacts at the time of the first episode of OM. In contrast, the infants with 2nd-yr ROM did not differ from the comparison group in the frequency of atopy. They had a large number of daily child contacts and were taken care outside the home during the 2nd yr of life; these were significant risk factors for ROM and for the recurrence.

Smoking by the parents may irritate the respiratory mucosa and so predispose to ROM (7, 18, 23) but today parents seem to be aware of this risk and avoid smoking at home or at least in the vicinity of the infant. Although parental smoking was not a risk factor for ROM, there were more smokers among parents of the infants with ROM than in the comparison group.

In our prospective study we tried to control and record all known confounding factors and we had detailed information about the feeding of the infants. We could study the simultaneous effect of many factors and identify independent risk factors for ROM by logistic regression analysis. These turned out to include no feeding variables. The mean durations of exclusive breast-feeding and of breast-feeding in general were similar in the infants with ROM and the comparison group. Thus prolongation of exclusive breast-feeding does not seem to afford added protection. All the infants were initially breast-fed and may have benefitted from this concerning the propensity toward ROM.

Table 5. *Plasma IgE concentrations (IU/ml) in infants with early-onset and 2nd-yr ROM and infants without OM (geometric mean and 95% confidence limits are given)*

Series	IgE at 6 mo	*n*	IgE at 9 mo	*n*	IgE at 12 mo	*n*
Infants with early-onset ROM	3.2 (1.3–7.9)	12	5.5 (1.6–18.7)	9	10.8 (3.9–30.0)	12
Infants with 2nd-yr ROM	1.3 (0.5–3.1)	8*	1.3 (0.6–2.9)	10	1.8 (0.7–4.7)†	12
Infants without OM	3.3 (2.2–5.0)	63	3.9 (1.8–8.0)	65	6.1 (4.3–8.8)	77

Significant differences between groups are indicated: * $p < 0.05$; † $p < 0.01$.

However, our study does not allow an evaluation of benefits of early breast-feeding. Neither short nor prolonged breast-feeding were risk factors for infantile atopy in our series (16). The total level of IgA was lower in the milk of the mothers whose infants became allergic to cow's milk than in mothers with nonallergic infants (24). Thus the quality of the breast milk may be more important in conferring resistance to disease than the duration of breast-feeding.

Cow's milk has been claimed to cause recurrence of OM in infancy either as an allergen (9) or as a direct irritant of the nasopharyngeal tubes in horizontal feeding (6). OM was more common in the infants with CMA than in the others, but only one of the infants with CMA developed ROM. Probably early detection of CMA with subsequent elimination diet and otorhinologic operations averted the cycle of infections. Another finding suggesting that cow's milk plays a role in ROM in some infants is the increased level of IgM antibodies to cow's milk in the plasma of these infants and the increased prevalence of supranormal levels of IgG antibody to cow's milk.

Our findings indicate that infantile ROM is associated with a number of predisposing factors. In some infants immune reactions are associated with cow's milk feeding. In infants developing ROM the most important risk factor in the 1st yr was their own atopy, in contrast to daycare outside the home and a large number of child contacts in the 2nd yr.

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Strachan, D.P., Jarvis, M.J., Feyerabend, C. "Passive smoking, salivary cotinine concentrations, and middle ear effusion in 7 year old children" Br Med J 298: 1549-1552, 1989.

This cross-sectional observational study was designed to assess the contribution of passive smoking to the development of middle ear underpressure and effusion. The subjects were 892 children aged 6.5-7.5 years taken from one-third of the primary schools in Edinburgh. Satisfactory tympanograms were obtained for 872 subjects, and results of assay of salivary cotinine concentrations were available for 770 children. Both measures were available in 736 of the original 892 children. The aim of this study was to determine if there was a correlation between the prevalence of middle ear underpressure and effusion and the salivary cotinine levels in the children. The authors reportedly found that there was a trend towards more abnormal tympanometric findings with increasing cotinine levels. The conclusion of the authors was that "[t]he results of this study are consistent with those of case-control studies of children attending for an operation to relieve middle ear effusion" and that "about one-third of the cases of middle ear effusion in this study were statistically attributable to exposure to tobacco smoke." The investigators recommend that "the disease should be added to the list of recognized hazards associated with passive smoking."

Passive smoking, salivary cotinine concentrations, and middle ear effusion in 7 year old children

D P Strachan, M J Jarvis, C Feyerabend

Abstract

Objective—To assess the contribution of passive exposure to tobacco smoke to the development of middle ear underpressure and effusion.

Design—Cross sectional observational study.

Setting—One third of the primary schools in Edinburgh.

Subjects—892 Children aged 6½ to 7½ were examined, and satisfactory tympanograms were obtained in 872. Results of assay of salivary cotinine concentrations were available for 770 children, and satisfactory tympanograms were available for 736 of these.

End point—Correlation of the prevalence of middle ear underpressure and effusion with concentrations of the marker of nicotine, cotinine, in the saliva of the children.

Measurements and main results—Middle ear pressure and compliance were measured in both ears by impedance tympanometry. Salivary cotinine concentrations were assayed by gas-liquid chromatography. Cotinine concentrations increased with the [redacted] concentration being 1·14 (95% confidence interval 1·03 to 1·27). After adjustment for the sex of the child and housing tenure the odds ratio for a doubling of the cotinine concentration was 1·13 (1·00 to 1·28).

Conclusions—The results of this study are consistent with those of case-control studies of children attending for an operation to relieve middle ear effusion. They indicate that the disease should be added to the list of recognised hazards associated with passive smoking. About one third of the cases of middle ear effusion in this study were statistically attributable to exposure to tobacco smoke.

Department of Community Medicine, University of Edinburgh, Edinburgh EH8 9AG
D P Strachan, MRCP, *Wellcome research training fellow in clinical epidemiology*

Addiction Research Unit, Institute of Psychiatry, London SE5 8AF
M J Jarvis, MPHIL, *senior lecturer*

National Poisons Unit, New Cross Hospital, London SE14 5ER
C Feyerabend, PHD, *senior chemist*

Correspondence to: Dr D P Strachan, Department of Epidemiology and Population Sciences, London School of Hygiene and Tropical Medicine, London WC1E 7HT.

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Introduction

Middle ear effusion (glue ear) is the commonest reason for admitting young children for an operation,[1] but little is known about its cause.[2] Case-control studies of children admitted for insertion of a grommet have shown an increased risk associated with the presence of smokers in the household,[3,4] particularly in children who had been exposed to high levels of tobacco smoke.[3] Criteria for referral and admission for middle ear effusion seem to be determined substantially by the "health culture" of the family[6] and by local clinical practice, which may in turn be affected by the availability of services.[7] Thus the interpretation of studies based on patients in hospital is complicated by selection bias, which may result in either a spurious relation with parental smoking or an underestimate of a true effect.[5]

Five studies of children in the general population have reported on the association between middle ear effusion and passive exposure to smoke.[8-12] Only Iversen *et al* found a significant association, and their results suggested that the risk associated with passive smoking increased with age.[9] If this is so it might explain the negative results of the other studies, which were based on children aged less than 5 years old.[8]

Both middle ear effusion and exposure to tobacco smoke can be measured objectively. Since its introduction some 20 years ago[13] impedance tympanometry has been widely used as a diagnostic and screening tool in young children, and its relation to fluid in the middle ear has been validated in patients attending for myringotomy.[14,15] Cotinine, an important metabolite of nicotine, is the most suitable marker to measure passive exposure to tobacco smoke. It is specific, has a half life of about 20 hours, and can be assayed in concentrations as low as 0·57 nmol/l (0·1 ng/ml) by gas-liquid chromatography.[16] Salivary concentrations of cotinine are roughly in proportion to those in blood and have been used to measure exposure to environmental tobacco smoke in adults[17,18] and adolescents.[19,20]

We investigated the relation between exposure to smoke and middle ear disease in a sample population of 7 year old schoolchildren who were participating in a survey of the effects of the home environment on respiratory health.[21]

Subjects and methods

A sample of one in three primary schools in Edinburgh was chosen at random, and the parents of all children in the third primary class (aged 6½–7½ years in September 1986) were contacted by postal questionnaire. This asked about respiratory symptoms and housing conditions relating to the child; more details are reported elsewhere.[21] The current or latest occupation of the head of the household was coded to a social class according to the registrar general's classification of occupations.[22] Written parental consent to clinical tests was requested, and ethical approval for the study was obtained from Lothian Health Board and Lothian Regional Council's education department.

Clinical tests were performed at the schools during January to June under the supervision of DPS. Middle ear pressure and compliance, the volume of the ear canal, and the relative gradient of the tympanometric curve were measured in both ears with a Microlab Earscan configured for impedance measurements (Micro Audiometrics, Florida, United States). This uses a probe tone of 226 Hz at 85 db and sweeps from 200 to −312 daPa at 100 daPa/s. The children were asked to swallow a sip of water immediately before the measurement was made to ensure that patent eustachian tubes would be ventilated. Table I shows the types of tympanograms, defined on the basis of the modification of Jerger's original classification[23] that was proposed

TABLE I—*Types of tympanograms according to Fiellau-Nikolajsen*[24]

Type	Middle ear pressure (daPa)	Gradient (%)	Interpretation
A	200 to −99·9	>10	Normal
C1	−100 to −199·9	>10	Mild underpressure
C2	−200 to −312	>10	Severe underpressure
B	No peak	<10	Middle ear effusion

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and validated by Fiellau-Nikolajsen.[1] To characterise each child the tympanogram obtained on examination of the more abnormal ear was used in the analysis.

The children were asked to collect saliva in their mouths and to spit into a clean plastic container. A sample of at least 1 ml was frozen within eight hours after collection for assay of cotinine concentration by gas-liquid chromatography.[21] Statistical analyses were performed by the statistical analysis system (SAS),[22,23] and logistic regression models were fitted by the generalised linear interactive modelling system (GLIM).[24] Tests for trend with one degree of freedom used the procedure proposed by Mantel[25] and implemented for stratified tabulations in the FREQ procedure in SAS.[23]

Results

The parents of 1095 children were sent a questionnaire, and 941 (86%) consented to their child being examined clinically. Twenty of these children left school before the survey was carried out, and a further 20 were included in pilot studies. Of the remaining 901 eligible children, 892 (99%) were examined, and satisfactory tympanograms were obtained for one or both ears in 872. In 23 children results were obtained for only one ear, but these were included in the analysis.

Table II shows the relation between findings on tympanometry and the sex of the child, social class, housing tenure, and number of smokers in the household. There was no significant difference in middle ear pressure with sex or social class (when this was known), but the prevalence of middle ear effusion (type B tympanogram) was higher in girls and among children of unknown social class. There was a significant trend towards abnormal tympanograms in the children whose parents were smokers, and the prevalence of effusion increased with the number of smokers in the household (χ^2 for trend in proportions =4·15, df=1, p<0·05). There was a similar trend, which was of borderline significance (p=0·051), associated with rented housing.

TABLE II—*Prevalence (%) of types of abnormalities on tympanometry of the more abnormal ear in 872 children aged 7 according to sex of child, socioeconomic state, housing tenure, and number of smokers in household. Numbers of children are given in parentheses*

	Middle ear pressure (daPa)				
	100 to −100 (type A)	−200 to −100 (type C1)	−300 to −200 (type C2)	No peak (type B)	χ^2 Trend*
Sex:					
Girls	63·1 (275)	17·0 (74)	12·4 (54)	7·6 (33)	
Boys	62·2 (271)	17·2 (75)	9·4 (41)	11·2 (49)	0·60
Social class of head of household:					
I	63·9 (62)	16·5 (16)	12·4 (12)	7·2 (7)	
II	63·9 (145)	14·5 (33)	14·5 (33)	7·1 (16)	
IIIN	62·4 (108)	21·4 (37)	5·2 (9)	11·0 (19)	0·00
IIIM	65·2 (118)	17·7 (32)	6·6 (12)	10·5 (19)	
IV/V	62·9 (66)	14·3 (15)	17·1 (18)	5·7 (6)	
Unknown†	52·8 (47)	18·0 (16)	12·4 (11)	16·9 (15)	
Tenure of housing:					
Owned	64·6 (396)	16·3 (100)	10·6 (65)	8·5 (52)	
Rented	57·8 (147)	18·5 (47)	11·8 (30)	11·8 (30)	3·80
No of smokers in household:					
0	63·9 (292)	17·3 (79)	10·7 (49)	8·1 (37)	
1	63·3 (169)	16·5 (44)	10·9 (29)	9·4 (25)	3·97‡
≥2	56·4 (79)	17·1 (24)	12·1 (17)	14·3 (20)	
Fifths of salivary cotinine (nmol/l):					
<0·57	64·8 (70)	15·7 (17)	12·0 (13)	7·4 (8)	
0·57–	72·6 (130)	13·4 (24)	8·9 (16)	5·0 (9)	
2·27–	65·4 (104)	20·8 (33)	5·7 (9)	8·2 (13)	7·01§
7·38–	61·0 (89)	17·8 (26)	6·9 (10)	14·4 (21)	
>19·9	58·3 (84)	16·7 (24)	12·5 (18)	12·5 (18)	

* df=1.
† Head of household was a student, a member of the armed forces, or had never been employed; this group was excluded from the test for linear trend.
‡ p<0·05. § p<0·01.

TABLE III—*Distribution of salivary cotinine concentrations according to number of smokers in household*

	Salivary cotinine (nmol/l)				
No of smokers in household	Minimum	First quartile	Median	Third quartile	Maximum
0 (n=405)	ND	ND	1·1	2·3	36·9
1 (n=241)	ND	4·5	10·2	22·7	205·0
≥2 (n=124)	2·3	12·5	25·0	37·5	97·1
Total (n=770)	ND	0·6	4·0	16·5	205·0

ND = None detected (<0·57 nmol/l).

The results of the salivary cotinine assay were available for 770 children (405 from non-smoking households, 241 from households with one smoker, and 124 from households with two or more smokers). Table III shows the distributions of salivary cotinine concentrations in these three groups. A total of 109 (27%) children from households with no smokers had concentrations below the limit of the assay (0·57 nmol/l), whereas only one child from a household with one or more smokers had no detectable salivary cotinine. Six children, five of them from households with only one smoker, had concentrations >82 nmol/l, a suggested cut off point to distinguish between smoking and non-smoking adults and adolescents.[26,27] These values were 93·1, 97·1, 106·2, 119·3, 144·8, and 205·0 nmol/l.

Table IV shows the relation between cotinine concentrations, sex of the children, and housing tenure within groups with similar numbers of smokers in the home.

TABLE IV—*Geometric mean salivary cotinine concentrations* (nmol/l) in 770 children aged 7 according to sex of child, housing tenure, and number of smokers in household. Numbers of children are given in parentheses*

	Tenure of housing			
	Owned		Rented	
No of smokers in household	Boys	Girls	Boys	Girls
0	0·85 (176)	1·02 (161)	3·01 (35)	8·63 (33)
1	5·62 (67)	6·53 (74)	17·04 (53)	25·95 (47)
≥2	15·61 (28)	17·04 (33)	21·47 (30)	34·36 (33)

* Undetectable concentrations were recorded as 0·28 nmol/l.

In view of the skewed nature of the distributions for cotinine concentrations the table gives geometric mean values. For logarithmic transformation undetectable concentrations were treated as 0·28 nmol/l. Female sex and rented housing were independently and consistently associated with higher cotinine concentrations given the same number of smokers in the household. These effects were apparent even in non-smoking households, and the difference with sex was particularly pronounced among children from rented homes.

Satisfactory tympanograms were obtained for 736 of the 770 children for whom we had data on salivary cotinine concentrations. When cotinine concentrations were grouped in fifths of the distribution there was a highly significant trend towards more abnormal tympanograms in the children with higher concentrations (table II). In view of the associations between cotinine concentrations and sex of the child and housing tenure and the modest effect of these factors on the prevalence of middle ear effusion the relation between salivary cotinine concentrations and abnormal tympanograms was analysed further by multiple logistic regression. Presence or absence of effusion (type B tympanogram) was treated as a dichotomous outcome variable. To investigate the form of the dose-response relation in more detail the data on cotinine concentrations were fitted as a continuous explanatory variable. The logarithm of the cotinine concentration was found to give the best fit, its relation to the prevalence of type B tympanograms being close to linear on a logarithmic scale (χ^2 for inclusion of quadratic term=0·0000, df=1).

In single factor models the odds ratio for female sex was 1·53 (95% confidence interval 0·92 to 1·98), and

for rented housing it was 1·43 (0·84 to 2·42). The effect of the logarithm of the cotinine concentration in a single factor model was significant ($\chi^2=6\cdot60$, df=1, $p<0\cdot02$), and the odds ratio for a doubling of salivary cotinine concentration was 1·14 (1·03 to 1·27). In a joint model including all three factors the effects of sex and logarithm of the cotinine concentration changed little, but there was an appreciable reduction in the odds ratio for children living in rented housing, suggesting that passive exposure to smoke accounted for much of the effect of rented housing in the single factor models. The adjusted odds ratios were 1·46 (0·87 to 2·44) for female sex, 1·03 (0·55 to 1·91) for rented housing, and 1·13 (1·00 to 1·28) for a doubling of salivary cotinine concentration. The effect of the logarithm of the cotinine concentration remained significant in the joint model ($\chi^2=4\cdot14$, df=1, $p<0\cdot05$). Further adjustment for parental social class, number of people living in a room, gas cooking, and the presence of damp walls in the home made no substantial difference to the coefficient for the logarithm of the cotinine concentration.

The linear relation between the logarithm of the cotinine concentration and the prevalence of middle ear effusion on a logit scale implied that the prevalence odds were proportional to a power of the cotinine concentration, the power exponent being the coefficient (logarithm of the odds ratio) for the logarithm (base e) of the cotinine concentration in the logistic model. The data suggested that the odds ratios for type B tympanograms after adjustment for sex and housing tenure relative to children with undetectable cotinine concentrations would be approximately 1·7 at 5·7 nmol/l (1 ng/ml) and 2·3 at 28·4 nmol/l (5 ng/ml). Thus even low levels of passive exposure to smoke may have substantial effects on the prevalence of middle ear effusion. The model predicted that in a population of the same distributions of age, sex, and tenure in which all children had undetectable cotinine concentrations the prevalence of type B tympanograms would be approximately 5·8%. As the observed prevalence was 9·4% at least one third of the cases of middle ear effusion in this age group may have been attributable to passive smoking.

Discussion

We believe that this is the first study to report biochemical data on passive exposure to smoke in primary school children. The age group chosen was young enough to exclude regular active smoking, but some of the higher concentrations of salivary cotinine observed were greater than could reasonably have been attributed to passive exposure. These high concentrations may indicate experimentation with cigarettes, even at this early age. None of the six children with cotinine concentrations above 82 nmol/l, however, had middle ear effusion (five had normal (type A) tympanograms), so their inclusion in the analysis will have tended to diminish any effects attributed to passive exposure to smoke rather than to generate a spurious effect.

As expected, cotinine concentrations were related to the number of smokers in the household, but equally striking was the variation with sex of the children and housing tenure within groups with the same numbers of smokers. Even among the children from non-smoking households cotinine concentrations were higher in those living in rented accommodation. This suggests that considerable exposure to smoke occurs outside the home, which is strongly related to social factors. When tenure and number of smokers were controlled for girls had higher salivary cotinine concentrations than boys. This may reflect differences in cotinine metabolism or in activity patterns, boys being perhaps more likely to play outdoors or away from adults who smoke. No difference with sex has been found in older children.[*]

The prevalence of abnormalities on tympanometry in this population of 7 year old children is consistent with previous reports.[**] Tympanometry was performed only once, and many of the abnormalities detected, including middle ear effusion, tend to resolve spontaneously.[*] This population survey probably included only a few cases of persistent disease in which an operation would be indicated. The findings are therefore complementary to, rather than directly comparable with, case-control studies of children admitted to hospital.[*] They do, however, relate to an age group close to the peak age for admission for an operation for middle ear effusion.[1]

Our results show a significant relation between salivary cotinine concentrations and disease of the middle ear, whether a range of abnormal tympanograms, or tympanograms with and without a definable peak (taken to indicate effusion) are considered. These associations were probably not due to bias because the measurements were objective and the laboratory analysts were blind to the tympanometric findings. Adjustment of the crude estimates of the effect of sex and housing tenure on cotinine concentrations indicated some confounding by these factors, but confounding by socioenvironmental factors probably did not persist in the final model. The coefficient for housing tenure in the joint model was small, and further adjustment for social class and a range of more specific housing characteristics made little difference to the results.

Salivary cotinine concentrations relate only to passive exposure to smoke in the previous two or three days, but Jarvis *et al* reported that over one year concentrations in non-smoking adolescent girls was reasonably stable.[*] Nevertheless, variation in exposure from week to week limits the reliability of a single measurement and the true association between passive smoking and middle ear effusion is therefore underestimated in our data.

The relation between passive exposure to smoke and middle ear effusion in the present study is more likely to be causal than due to chance, bias, or confounding factors. The common mechanism in the development of serous otitis media is considered to be loss of patency of the eustachian tube, to which anatomical factors, impaired mucociliary function, and upper respiratory infection or allergy may contribute.[*] Passive smoking may increase the risk of blockage of the eustachian tube in three ways: by directly impairing mucociliary function, by causing congestion of the soft tissues of the nasopharynx, or by predisposing people to upper respiratory infection. Because this was a study of the prevalence of middle ear effusion we cannot draw conclusions about whether exposure to smoke influences the incidence or the persistence of the disease.

Concern has been expressed recently that the documented risks of passive smoking have not included middle ear effusion.[*] In view of the important burden on the health service imposed by this disease and suspicions of its long term effects on linguistic and cognitive development,[*] middle ear effusion in children should be regarded as one of the more important hazards attributable to environmental tobacco smoke.

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Relation between mortality and treated blood pressure in elderly patients with hypertension: report of the European Working Party on High Blood Pressure in the Elderly

J Staessen, C Bulpitt, D Clement, P De Leeuw, R Fagard, A Fletcher, F Forette, G Leonetti, A Nissinen, K O'Malley, J Tuomilehto, J Webster, B O Williams

European Working Party on High Blood Pressure in the Elderly
Collaborating centres are listed at the end of this paper. Manuscript prepared by J Staessen and A E Fletcher

Correspondence to: Dr J Staessen, Klinisch Laboratorium Hypertensie, Inwendige Geneeskunde-Cardiologie, University Hospital Gasthuisberg, B-3000 Leuven, Belgium.

Br Med J 1989;298:1552-6

Abstract

Objective—To investigate the relation between mortality and treated systolic and diastolic blood pressures.

Design—Randomised double blind placebo controlled trial. Mortality in the two treatment groups was examined in thirds of treated systolic and diastolic blood pressures.

Patients—339 And 352 patients allocated to placebo and active treatment, respectively. The groups were similar at randomisation in sex ratio (70% women), mean age (71·5 years), blood pressure (182/101 mm Hg), and proportion of patients with cardiovascular complications (35%).

Measurements and main results—In the placebo group total mortality rose with increasing systolic pressure whereas it had a U shaped relation with diastolic pressure, the total lowest mortality being in patients in the middle third of the distribution of diastolic pressure. In the group given active treatment total mortality showed a U shaped relation with systolic pressure and an inverse association with treated diastolic pressure. In both groups cardiovascular and non-cardiovascular mortality followed the same trends as total mortality. The increased mortality in the lowest thirds of pressure was not associated with an increased proportion of patients with cardiovascular complications at randomisation or with a fall in diastolic pressure exceeding the median fall in pressure in each group. In contrast, patients in the lowest thirds of pressure showed greater decreases in body weight and haemoglobin concentration than those in the middle and upper thirds of pressure.

Conclusions—In patients taking active treatment total mortality was increased in the lowest thirds of treated systolic and diastolic blood pressures. This increased mortality is not necessarily explained by an exaggerated reduction in pressure induced by drugs as for diastolic pressure a U shaped relation also existed during treatment with placebo. In addition, patients in the lowest thirds of systolic and diastolic pressures were characterised by decreases in body weight and haemoglobin concentration, and the patients in the lowest thirds of diastolic pressure taking active treatment also by an increased non-cardiovascular mortality, suggesting some deterioration of general health.

Introduction

Several large studies of hypertension have recently been reviewed.[1 2] The observation in these studies of a J shaped relation between the risk of myocardial infarction and treated blood pressure[3-9] has led to the suggestion that a reduction of pressure induced by drugs might cause as well as prevent myocardial ischaemia.[3 10 11] None of the studies was placebo controlled, and other large hypertension-mortality intervention trials have either not confirmed[12-14] or not reported[15 16] this J shaped relation. In the international prospective primary prevention study in hypertension all patients received active drugs but patients with overt ischaemic heart disease were excluded[16]; there was no evidence for a J curve. In contrast, Coope and Warrender found that total mortality and deaths from myocardial infarction showed a J shaped relation with the diastolic pressure attained in elderly patients with

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undecided.[1] I found similar responses amongst a random sample of 1000 general practitioners in New Zealand: 22% reported that informed consent for testing was not at all important and 4% were undecided. I, too, found that years since graduation was a significant variable as was the number of patients requesting an HIV test. Younger doctors and those with the most requests for tests believed more strongly in informed consent.

In addition I examined attitudes to anonymous testing and to confidentiality. Anonymous testing, although recommended and widely practised in New Zealand, was disagreed with by 28% of the sample, including 7% who disagreed strongly. In fact, only 41% agreed with it, the remainder being neutral. Attitudes to confidentiality were shown by the doctors' responses to questions on sharing information about patients with AIDS. Sixteen per cent of the doctors would give such information to reception staff, and the same proportion would give it to colleagues outside the practice. Women doctors were less likely to do this than men.

It is worrying that the findings of this study and those of Dr Shapiro show some indifference to major issues regarding patients' rights such as informed consent and anonymous testing. This is particularly sad given the crucial role that general practitioners will have in the future in caring for those with AIDS or HIV infection and their families. Such indifference will inevitably lead to mistrust on the part of patients and to a reluctance to seek help from general practitioners when it is needed. Future efforts in educating general practitioners about HIV must address these matters.

JANE CHETWYND

University Department of Community Health
and General Practice,
Christchurch School of Medicine,
Christchurch,
New Zealand

1 Shapiro JA. General practitioners' attitudes towards AIDS and their perceived information needs. *Br Med J* 1989;298:1563-6. (10 June.)

Passive smoking and middle ear effusion in children

SIR,—Dr D Strachan and colleagues presented an interesting report on the possible association of passive smoking with otitis media with effusion,[1] but there are three points that need addressing before their conclusions can be reached.

Eustachian tube dysfunction is extremely common in children and gives rise to negative middle ear pressure and middle ear effusion. The prevalence of middle ear effusion varies inversely with age, but there is also a marked seasonal variation, possibly related to a similar variation in upper respiratory tract infections.[2] The authors have quite rightly confined themselves to a single age group, but they carried out their tests over a period from January to June. Those tested earlier should have a higher rate of abnormal results, but this is not taken into account in the analysis.

Perhaps more importantly they fail to indicate whether the children had already had ear, nose, and throat operations (which at the age of 7 must be a considerable percentage) or whether there were other important factors such as cleft palate or Down's syndrome.

As otolaryngologists we deplore the use of tympanometry alone in the diagnosis of middle ear disease. It is a useful screening test, but in the presence of an abnormal finding we believe otoscopy must be performed. Frequently an obvious cause for the flat tympanogram such as wax, perforation, or even a grommet will be found. Dr Strachan and colleagues unfortunately do not seem to have checked their findings with otoscopy.

A possible indicator of this fault can be found in their numbers of abnormal tympanograms with increasing cotinine concentrations. There seems to be a trend relating increasing incidence of flat tympanograms to cotinine concentration, but there is no such trend with negative middle ear pressure. If one assumes that the same pathological process causes both negative middle ear pressure and middle ear effusion through dysfunction of the eustachian tube then the association between passive smoking and middle ear effusion is quite likely to be spurious.

It seems a pity that a paper written by an epidemiologist, a psychiatrist, and a chemist about an ear, nose, and throat condition should not have had the very necessary skills of an otolaryngologist to validate its findings.

C J WOODHEAD
R M TERRY

Department of Ear, Nose, and Throat Surgery,
Seacroft Hospital, Leeds LS14 6UH

1 Strachan DP, Jarvis MJ, Feyerabend C. Passive smoking, salivary cotinine concentrations, and middle ear effusion in 7 year old children. *Br Med J* 1989;298:1549-52. (10 June.)
2 Hinchcliffe R, Prasansuk S. Epidemiology and SOM. A review. *Scand Audiol (Suppl)* 1986;26:53-8.

AUTHORS' REPLY,—Impedance tympanometry may not be the definitive diagnostic test for middle ear diffusion, but most previous epidemiological surveys have relied on this technique. Tympanometric measurement of the physical volume of the ear canal guards against the common sources of error. High values (>2·0 ml) indicate a perforated eardrum or patent ventilation tube, and in the seven children with such abnormality we conservatively chose to analyse the tympanogram from the other ear. No results were recorded from ears with blockage of the probe or low physical volume (<0·5 ml) suggesting wax. It is unlikely that flat tympanograms attributable to impacted wax could have generated a spurious association with passive exposure to smoke.

Children whose tonsils or adenoids had been removed (n=104) were at substantially higher risk of middle ear effusion (22% v 8%). Such a history was unrelated to the presence of smokers in the household (12% v 13%), so it is unlikely that previous surgical treatment affected the observed relation between middle ear effusion and passive exposure to smoke.

Different relations of passive smoking to type C and type B tympanograms might be expected if tobacco smoke affects the persistence of effusions rather than their incidence. In fact, normal (type A) tympanograms were less common in the children with higher cotinine concentrations, so that among the children without effusion there was a slightly higher risk of reduced middle ear pressure with heavy exposure to smoke (table II in our paper).

Month of examination would not affect the association between tympanometric findings and the number of smokers in the household, which was ascertained by a simultaneous questionnaire survey, but it was a potential confounding variable in our analysis of middle ear effusion and salivary cotinine concentrations. The prevalence of type B tympanograms was higher among children tested in January or February (12%) than in March or April (10%) and May or June (7%). After adjustment for sex, housing tenure, and number of smokers in the household the geometric mean salivary cotinine concentration in January and February was approximately double that in May and June. Nevertheless, the relation between middle ear effusion and the logarithm of the cotinine concentration remained significant after adjustment for month of examination (odds ratio per doubling 1·12; 95% confidence interval 1·01 to 1·25, χ^2=4·30, df=1). Indeed, after adjustment for log cotinine the trend in prevalence by month of examination was non-significant (χ^2 (trend)=1·07, df=1). Greater indoor exposure to tobacco smoke during the winter may contribute to the seasonal variation in prevalence of middle ear effusion.

D P STRACHAN
M JARVIS
C FEYERABEND

Department of Epidemiology and
Population Sciences,
London School of Hygiene and Tropical Medicine,
London WC1E 7HT

SIR,—I agree with Dr D P Strachan and colleagues that middle ear effusions in children should be recognised as one of the hazards of passive smoking.[1] It has been recognised for some time that passive smoking may have deleterious effects on the respiratory tracts of children. It is only recently that the adverse effects of passive smoking on the middle ear have been reported.

Not only is passive smoking in children associated with a higher than expected incidence of middle ear effusions and abnormal results of tympanometry[2] but these children are put at an increased risk of undergoing surgery for the condition. There is an increased incidence of grommet insertion and adenoidectomy in children whose parents smoke. Such children are twice as likely to require adenoidectomy, and their chance of requiring grommet insertion is increased by half.[3]

It is important to impress upon smoking parents that they may be subjecting their children not only to a greater risk of middle ear effusions but also to an increased likelihood of surgical intervention for the condition with the possibilities of both physical and psychological complications.

ANTHONY HINTON

Department of Otolaryngology,
Manchester Royal Infirmary,
Manchester M13 9WL

1 Strachan DP, Jarvis MJ, Feyerabend C. Passive smoking, salivary cotinine concentrations, and middle ear effusion in 7 year old children. *Br Med J* 1989;299:1549-52. (10 June.)
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Transurethral prostatic resection: a safe operation

SIR,—I was intrigued by Mr G Williams and colleagues' use of an expandable metal mesh stent for treating prostatic obstruction in patients considered unfit for transurethral prostatic surgery.[1] I was surprised, however, by their statement that the mortality associated with transurethral resection of the prostate has "led to a search for less invasive treatments," thus prompting this innovation.

Equally surprisingly, Mr Williams and colleagues were presented (in a short time, it would seem) with nine patients who were considered unfit for prostatic resection and hence were offered a stent as alternative treatment. Although the authors did not indicate the timespan over which these cases were collected, it could not have been very great as the first urological use of these stents was reported only in 1988. Accordingly the nine patients considered unfit for transurethral resection would seem to represent an uncharacteristically high proportion of all patients referred for prostatic surgery during this relatively short period. All this is at odds with my experience and that of my colleagues. I work in a 590 bed teaching hospital. In the 12 months to March 1989, 328 transurethral resections of the prostate were performed by the urology unit. None of the patients died, and only one patient with severe ischaemic heart disease was advised that he was unfit for surgery.

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Zielhuis, G.A., Heuvelmans-Heinen, E.W., Rach, G.H., Van Den Broek, P. **"Environmental risk factors for Otitis Media with Effusion in preschool children"** Scand J Prim Health Care 7(1): 33-38, 1989.

SUMMARY: To ascertain risk factors for otitis media with effusion (OME), a cohort of 1439 preschool children, 2 years of age, was investigated by means of tympanometry at 3-monthly intervals until their fourth birthday. Parents were asked about potential risk factors for OME. Data were analysed in a case-control design with incident cases. Age, season, family size, siblings's [sic] history of OME, frequent swimming, duration of breast feeding and public day care appear to have a significant effect on OME, even after adjustment for nasal infection. Gender, race, birth weight and passive smoking were not related to OME incidence. With the exception of age and season, the relative risks of environmental factors for OME are always very low. It is concluded that the study of environmental risk factors for OME is necessary to increase the knowledge of the nature of this disease, but that it does not contribute much to medical care at the moment.

Scand J Prim Health Care 1989; 7/33–8

Environmental Risk Factors for Otitis Media with Effusion in Preschool Children

GERHARD A. ZIELHUIS,[1] ELS W. HEUVELMANS-HEINEN,[1] GEROLD H. RACH[2] and PAUL VAN DEN BROEK[2]

Department of Epidemiology, Department of Otorhinolaryngology, University of Nijmegen

Zielhuis GA, Heuvelmans-Heinen EW, Rach GH, van den Broek P. Environmental Risk Factors for Otitis Media with Effusion in Preschool Children. Scand J Prim Health Care 1989: 7: 33–8.

To ascertain risk factors for otitis media with effusion (OME), a cohort of 1439 preschool children, 2 years of age, was investigated by means of tympanometry at 3-monthly intervals until their fourth birthday. Parents were asked about potential risk factors for OME. Data were analysed in a case-control design with incident cases. Age, season, family size, siblings's history of OME, frequent swimming, duration of breast feeding and public day care appear to have a significant effect on OME, even after adjustment for nasal infection. Gender, race, birth weight and passive smoking were not related to OME incidence. With the exception of age and season, the relative risks of environmental factors for OME are always very low. It is concluded that the study of environmental risk factors for OME is necessary to increase the knowledge of the nature of this disease, but that it does not contribute much to medical care at the moment.

Key words: otitis media with effusion, secretory otitis media, epidemiology, risk factors, preschool children.

G. A. Zielhuis, Department of Epidemiology, Institute of Social Medicine, Verlengde Groenestraat 75, 6525 EJ NIJMEGEN, The Netherlands.

INTRODUCTION

Otitis media with effusion (OME = secretory otitis media = glue ear) is one of the commonest diseases in childhood and is responsible for most of the hearing losses in this age group (1–3). Because of its silent nature – the disease remains unnoticed on many occasions – those who come to the attention of a general practitioner, paediatrician, ENT surgeon, or a public health officer form only the tip of the iceberg (4). OME has been studied world-wide, with respect to its epidemiology, natural course, diagnosis, sequelae, treatment, and risk factors.

Studying risk factors for OME is important for several reasons. First, it can give clues to the better understanding of the aetiology of the disease. This may indicate possibilities for (primary) prevention. Second, if screening is considered for OME, knowledge of risk factors may lead to the definition of high-risk groups, which should receive priority in such a screening programme. And third, knowledge of risk factors may help doctors (GPs and others) to make a diagnosis. Such information might help to complete the clinical picture and lead to a valid diagnosis of OME.

A large amount has been written about risk factors for OME. The effect of upper respiratory tract (URT) infections on tubal function and middle ear status is widely documented and no object for dispute. Children with pathology of the URT, such as simple rhinitis, run an increased risk of developing OME (5–7). The prognostic value is much less clear for the other (environmental) risk factors. Studies on this topic often give contradictory results, perhaps because of methodological shortcomings, such as invalid measurements, small sample sizes, and lack of correction for interdependencies between risk factors.

In reviewing epidemiological studies that meet some basic scientific standards (i.e. tympanometry

measurement or pneumatic otoscopy: sufficient sample size, no overt bias), we can list ten risk factors:

- *Age*. The prevalence of OME at birth is assumed to be zero. The occurrence starts to rise after 6 months, and reaches a maximum at about two years of age. The prevalence then decreases, with a small elevation at about five years. From the age of seven, OME is relatively rare. Exposure to respiratory infections is thought to be related to this typical age structure (8–10).
- *Gender*. Many studies (11, 12), but not all (5), have found a higher prevalence of OME in boys. Again this difference could be related to differences in genetic susceptibility to infections (13).
- *Race*. Some specific populations, such as Eskimos, Indians, gypsies, and Australian Aboriginals are known to have higher prevalences of OME (14–16). This predominance can partly be explained by socio-hygienic conditions. Shurin et al (17) found that white children are three times more susceptible to persistent OME than black children. This can partly be explained by the higher level of medical observation and therefore the greater chance of detection in white children.
- *Family characteristics*. Family size is probably not a major risk factor for OME (18). There is conflicting data on the relevance of a family history of ear diseases or atopic diseases (5, 18, 19). There is no agreement about the importance of socio-economic status as a risk indicator for OME. If an effect exists, it is probably not due to malnourishment (5, 20) but to poor housing conditions and crowding (21).
- *Pregnancy and lactation*. Although many studies (22) show a relation between the way an infant is fed (breast/bottle) and respiratory illness the evidence for an effect of feeding practice on OME is scanty and conflicting (18, 23). The same is true for birth weight and prematurity as risk indicators for OME (24, 25).
- *Season and climate*. Higher incidences in cold seasons have been widely described (11, 24), but there is only scant evidence that specific climatic conditions are responsible for this seasonable variation.
- *Swimming*. Although it has been put forward as a risk factor, swimming has not proved to be an important prognostic factor (25).
- *Public day care*. A considerable amount of evidence on the frequency of OME has been published on the effect of exposure to other children (8, 26–28). Again, this effect could be explained by respiratory infections.
- *Passive smoking*. There is little evidence that parental smoking has an effect on the risk for OME, but the literature is not consistent (21, 29).
- *Constitution and congenital abnormalities*. Children with Down's syndrome, cleft palate, or Kartagener's syndrome are more at risk for OME compared with children without these congenital defects (15, 30).
  The literature on the risk for OME in children with atopic constitution or allergy is inconclusive (5, 18, 19).

This review of the limited evidence available on risk factors for OME calls for further studies that cope with methodological fallacies. The present paper describes a large-scale epidemiological study on the prevalence of OME in preschool children, in which the various possible risk factors have been investigated.

POPULATION AND METHODS

The KNOOP project is a large-scale epidemiological study on the natural history of OME in preschool children, performed in the city of Nijmegen. All children born between 1 September 1982 and 31 August 1983 and living in Nijmegen on their second birthday were included. The group comprised 1439 children, from whose parents permission to take part in the study was sought. Tympanometry (Grason Stadler-27) was performed at three-monthly intervals, from the children's second birth-day until four years of age. All measurements were carried out by trained audiological assistants at the children's home address. The tympanograms of all ears were classified into four types (modification of Jerger 1970).

type A : maximum compliance ≥0.2 ml at a middle ear pressure -99 to +200 dPa
type C1: maximum compliance ≥0.2 ml at a middle ear pressure -199 to -100 dPa
type C2: maximum compliance ≥0.2 ml at a middle ear pressure -399 to -200 dPa
type B: maximum compliance <0.2 ml or at a middle ear pressure ≤-400 dPa.

Type B indicates the presence of middle ear effusion. At each of the nine consecutive tympanometric

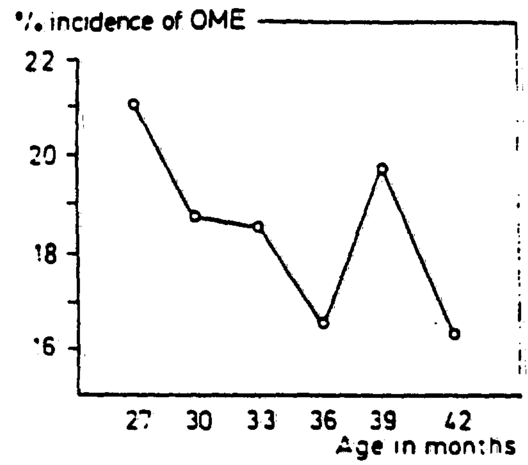

Fig. 1. Relation between age and the 3-monthly incidence of OME. Results of the KNOOP project.

screenings, the parents were asked about potentially relevant events during the three previous months, including possible risk factors for OME.

To study the effect of the factors on the risk for OME, we selected incidence data with reference to all children who did not have a type B tympanogram at a particular screening. Children in this group were considered to be patients when at least one ear showed a type B tympanogram at the next screening. The control group consisted of children with a type A tympanogram in both ears, or a combination of type A and type C1 tympanograms at this latter screening. These two groups form the basis for a case-control analysis.

Regarding family characteristics, passive smoking, type of day care, and swimming, we selected incidence data from the screening session in which the parents were asked about these factors, i.e. when the children were 27, 30, 36 and 42 months of age, respectively (sessions 2, 3, 5 and 7, respectively).

To study the effect of age, we included the data from all screening sessions until the age of 42 months. The percentage of children with at least one B tympanogram at a particular session was calculated from all children without a type B tympanogram at the former screening.

Incidence data on the other risk factors were collected at the age of 42 months. This approach is based on the assumption that risk-factor information collected at other ages will give valid estimates of the status at 42 months of age. The relative risk for all risk factors was estimated by means of an odds ratio (OR) with a 95 % confidence interval (CI). Hypotheses of elevated risk ratios were tested by means of the chi-square test. A stratified analysis was performed to take URT infections into account as a confounder, in situations where the OR was significantly above unity. Stratification was performed by dividing the study population into two groups: one group in which the children had had a serious nasal infection during the previous three months and a second which had not.

RESULTS

Figure 1 shows the relation between age and the three-monthly incidence of children with OME (= type B tympanogram). A bimodal curve with one peak at the age of 27 months and another at 39 months can be seen.

Patients and controls did not differ significantly with respect to the distribution of race, parental history of OM, breast feeding, gestation period, birth weight, and smoking by household members (Table 1). However, the following factors seem to bear a pertinent relation to the occurrence of OME.

The longer a child had been breast fed, the less the risk for OME. This trend appeared to be significant ($p < 0.05$). The risk for OME in boys was 1.5 times higher than in girls.

Family size and a history of OME in siblings were significantly related to the incidence of OME.

Season was an important factor in the aetiology of OME. With the summer as reference point, the highest risk for OME was found in winter, the smallest elevated risk in spring.

No overall association between swimming and OME could be found. Only frequent swimming, at least once a week, showed an elevated risk for OME. There was no linear trend for the frequency of swimming.

Attending public day care enhanced the occurrence of OME, but there was no linear trend in the effect of time spent at public day care.

Ten children in this study population suffered from congenital pathology of very diverse origins, and its role in the aetiology could not therefore be established.

Nasal infection appeared to be a confounder of all the significant risk factors mentioned above. After adjustment for nasal infection, all other risk factors remained (see Table I). The confounder effect was strongest for public day care.

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Table 1. *Risk factors for OME, with and without correction for upper respiratory tract infections.*

Environmental risk factors	No. of cases	No. of contr.	OR	p	OR*	p*
gender (m/f)	117	386	1.50	0.055	-	-
race (European/not European)	116	368	1.75	0.219	-	-
family size (1, 2, ≥3 children)	140	354	-	0.010	-	0.002
parental history OME (y/n)	140	354	0.80	0.303	-	-
siblings history OME (y/n)	140	354	1.85	0.005	1.66	0.024
breast feeding (n/y)	115	366	0.71	0.187	-	-
duration of breast feeding						
(0–4 wks/2–3 m/4–6 m/≥7 m)	86	250	-	0.176	-	-
2–3 months/0–4 weeks	35	136	1.07	0.865	-	-
4–6 months/0–4 weeks	37	110	0.64	0.234	-	-
≥7 months/0–4 weeks	46	124	0.57	0.113	-	-
gestation period						
(≥38 weeks/<38 weeks)	117	386	0.74	0.354	-	-
birth weight						
(≤2500 gr/>2500 grams)	114	382	1.61	0.190	-	-
season						
autumn/winter/spring/summer	117	386	-	0.000	-	0.007
spring/summer	42	208	2.35	0.012	1.61	0.184
autumn/summer	47	215	2.59	0.004	2.19	0.019
winter/summer	60	209	3.93	0.000	2.84	0.002
swimming (last 3 months)						
(no/1–3×/4–11×/≥12×)	117	345	-	0.068	-	-
≥1×/no	117	345	1.14	0.552	-	-
1–3×/no	82	248	1.14	0.640	-	-
4–11×no	72	245	0.70	0.275	-	-
≥12×/no	79	216	1.94	0.034	2.38	0.009
public day care						
(y/n)	122	337	1.88	0.007	1.71	0.023
no. of half days a week						
(1–2/3–4/≥5)	122	393	-	0.003	-	0.348
3–4/1–2	80	188	1.11	0.711	-	-
≥5/1–2	89	320	0.50	0.004	0.73	0.207
smoking by household members (y/n)	128	307	1.11	0.643	-	-
no. of cigarettes per day						
(0/1–7/8–17/18–27/≥28)	127	304	-	0.274	-	-
8–17/1–7	44	76	1.24	0.599	-	-
18–27/1–7	32	89	0.60	0.236	-	-
≥28/1–7	30	71	0.76	0.527	-	-

* Corrected for nasal infection by means of the method of Mantel and Haenszel in case the crude odds ratio was significantly ($p < 0.05$) above unity.

DISCUSSION

Of all the environmental risk factors studied, only a few appeared to have a significant effect on OME: age, season, family size, sibling's history of OM, frequent swimming, and public day care.

The literature also suggests a bimodal curve for the prevalence of OME according to age (10), but in the curve we found (using incidence data) the second peak occurred at an earlier age. This indicates a faster rate of normalization of OME at about the age of 39 months. The development of the Eustachian tube and the level of maturity of the immune system may explain this.

Our finding that the highest rates of OME occurred during winter, and the lowest during the summer is in agreement with previous studies (9, 11). After adjustment for common colds, there was still a significant relationship between season and OME, but only for autumn and winter seasons. In the context of the KNOOP-project, the connection between OME and weather conditions has been studied (31). Low temperatures and few hours of sunlight appeared to be relevant factors.

According to the literature, the family history of OME (parents or siblings) is predictive for the occurrence of OME. Our data, however, showed only a significant relation with family size and history of OM in siblings. Our implication of the type of day care in the aetiology of OME agrees with other authors (8, 26–28). However, the trend in our study for the more time children are exposed to other children, the more they develop OME, was not significant. All these results seem to indicate that OME is a contagious disease.

It was shown by Ishidoya et al (25), as in our project, that swimming was not an important risk factor. Only frequent swimming, at least once a week, showed some effect in our data. More studies, which consider the swimming environment and the type of swimming water as well, are necessary to establish the specific effect of swimming behaviour.

In spite of our criticism of other studies in the introduction, we did not perform multivariate analyses. But, due to the design of the study, age and season are uniformly distributed among the other factors. The other risk factors we found to be significant are independent of each other on account of their nature.

It is generally accepted that URT infections play an important role in the pathogenesis of OME and therefore are a potential confounder in risk factor analyses. Surprisingly, we found that the effect of risk factors on the incidence of OME remained significant after correction for URT infections. However, it should be noted that we adjusted for nasal infection in the preceding three months, before a case of OME was diagnosed. This may have caused some misclassification and thereby incorrect confounder control.

That we could not find a significant effect for the remaining risk factors does not necessarily mean that they have no effect on OME. Further in-depth studies, in which a direct relationship between nasal infections and OME must be taken into account, are necessary to clarify the effect of these factors on OME.

It should be noted that the relative risks of environmental risk factors, with the exception of age and season, were always very low, though sometimes significant. This has relevance in the context of preventive and clinical practice.

- With such low relative risks, it is impossible to reduce the OME incidence substantially by means of (primary) prevention. Moreover, these factors do not lend themselves to intervention strategies.
- If a screening program for OME is considered, it should be realized that the risk factors found do not lead to a clear definition of high-risk groups, i.e. groups that contain most of the OME cases.
- In the context of OME diagnosis, knowledge of risk factors has a low predictive value. The only environmental factors strong enough to justify inclusion in medical decisions are age and season.

This means that studying environmental risk factors for OME is mainly a scientific activity that could help to increase our knowledge of the nature of the disease, without making a significant contribution to medical care at the moment.

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Pukander, J., Sipila, M., Kataja, M., Karma, P. "Estimating the Risk of Acute Otitis Media Among Urban Children" Ann Otol Rhinol Laryngol Supplement 99(149): 18-20, 1990.

The present study comprised a cohort of 1,294 children followed from the age of 7 months to the age of 2 years. Epidemiologic data were collected during the children's regular checkup visits at child health-care centers, and their ears were examined and, if necessary, treated in specific study clinics. The "overwhelmingly highest risk indicator" was day-care outside of the home. The results of this study suggest that a mother's smoking may increase most the risk to the baby of contracting acute otitis media and especially of recurrent attacks of otitis media. The authors conclude that "the best place for a small child during the first years of life is in his own house were the mother breast-feeds him and does not smoke."

TABLE 7. AGE AT FIRST EPISODE OF AOM IN RELATION TO NUMBER OF EPISODES OF AOM PER CHILD

No. of Episodes per Child	Age at First Episode							
	<1 yr		1 yr		≥2 yr		Total	
	No.	%	No.	%	No.	%	No.	%
1	295	28	407	41	650	69.0	1,352	45
2-3	430	41	411	42	257	27.5	1,098	37
4-5	200	19	128	13	30	3.0	358	12
6-16	130	12	35	4	5	0.5	170	6
Total	1,055	100	981	100	942	100.0	2,978	100

AOM — acute otitis media.

among children born in 1977 and living in different districts and different types of houses in the city of Malmö was studied in three different districts (center of the city, Rosengård, and Oxie). In the center of the city most families live in older, mainly well-maintained apartment houses. Rosengård is a modern crowded tenement house district built in the 1960s and 1970s. Oxie is a modern crowded villa suburb outside Malmö built in the later 1970s. The children living in Oxie had the highest cumulative incidence rate. At the end of the observation period of 5 years, about 65% of the children had had at least one episode of acute otitis media with effusion. The corresponding figures for the children living in Rosengård and in the center of the city were about 55% and 45%, respectively. The differences among the districts were significant ($p < .001$).

In order to study the importance of day-care type and the importance of age at first episode to the total number of episodes per child, 2,978 children were followed during their first 4 years of life. The children were born from 1977 to 1979 and had been registered for at least one episode of acute otitis media. Among children attending public day-care centers for the first time before the age of 2 years, 8% were registered for six or more episodes of acute otitis media during their first 4 years of life. In children attending public day-care centers for the first time between the ages of 2 and 3 years, 5% had six or more episodes of acute otitis media during the corresponding time. For children cared for at home or privately during their first 4 years of life, 3% were registered for six or more episodes of acute otitis media. The difference between the groups was statistically significant ($p < .001$).

Table 7 shows the age at the first episode of acute otitis media in relation to the total number of episodes per child during the first 4 years of life. Forty-five percent of the children had only one episode, while 6% were registered for six or more episodes. Among 1,055 children having their first episode of acute otitis media before the age of 1 year, 12% were registered for six or more episodes. The corresponding figure among 942 children having their first episode after the age of 2 years was 0.5%. The difference between the groups was significant ($p < .001$).

The study of the medical records of 504 children from the otolaryngology and pediatric departments showed that the otitis-prone children were registered for a mean number of 39 ambulatory visits per child during their first 4 years of life, as compared to 9 visits per child in the control group.

In the otitis-prone group myringotomy was performed at least once in 67% of the children. Fifty-two percent had tympanostomy tubes inserted and 19% had undergone adenoidectomy. The corresponding figures from the control group were myringotomy, 13%; tympanostomy tubes, 6%; and adenoidectomy, 6%.

The occurrence of other diseases diagnosed in the children showed that in the otitis-prone group, 53% had been found to have bronchopulmonary diseases at least once, 44% had been treated for gastrointestinal diseases, and 36% had been found to have allergic symptoms or diseases at least once. The corresponding figures for the control group were bronchopulmonary diseases, 32%; gastrointestinal diseases, 33%; and allergic symptoms or diseases, 17%. The difference between the two groups was statistically significant ($p < .001$).

CONCLUSIONS

The incidence rate of acute otitis media was highest in 1-year-old boys. At the age of 3 years, about 50% of all children in Malmö had had at least one diagnosed episode of acute otitis media. At the age of 7 years, the corresponding figures were 65% to 70%.

The incidence of acute otitis media was found to vary among children living in different districts and in different types of housing in the city. Children attending public day-care centers early in life were more prone to recurrent episodes of acute otitis media than those attending public day-care at later ages, or those children cared for at home or in private care.

Children having their first episode of acute otitis media before the age of 1 year run a greater risk of being otitis-prone than those having their first episode after the age of 1 year. Children with recurrent episodes of acute otitis media early in life also seem to be more prone than other children to other kinds of diseases, ie, bronchopulmonary, gastrointestinal, and allergic diseases.

It is important to detect and recognize otitis-prone children as early as possible in order to be able to offer them treatment and long-range control.

ESTIMATING THE RISK OF ACUTE OTITIS MEDIA AMONG URBAN CHILDREN

JUHANI PUKANDER, MD; MARKKU SIPILÄ, MD; MATTI KATAJA, PHD; PEKKA KARMA, MD

Acute otitis media is an increasingly important health problem among the pediatric population. Only a few children escape acute otitis media during their childhood days.[47] Many factors may affect the liability of a small child to contract acute otitis media. These factors are undergoing continuous change along with changes in the way of living and behavior of the entire society. One of the most prevalent changes is the arrangement of day-care for children, because increasingly both parents are working outside the home.[48]

TABLE 8. STEPWISE MULTIVARIANT ANALYSIS OF INTERRELATED POWER FUNCTION OF VARIABLES AFFECTING OCCURRENCE OF AOM AMONG 1,294 CHILDREN

	Rank of Importance Along With Minimum No. of AOM Attacks per Child					*Correlation Coefficient (r) of Separate Variables Affecting Occurrence*	
	1	*2*	*3*	*4*	*5*	*Children With at Least 1 AOM Attack (no/yes)*	*Total No. of AOM Attacks per Child*
Attending day-care center	1	1	1	1	1	0.161*	0.263*
Sibling(s) with AOM attacks during follow-up	4	2	2	2	2	0.129*	0.142*
Attending family day-care	8	4	5	3	9	0.068†	−0.009
Type of housing	3	6	9	9	7		
Smoking of parent(s)		8	6	4	4		
Mother's respiratory infections before follow-up	5	3	11	11		0.062	0.023
Birth weight	15	11	3	10	10	0.032	0.009
Father's respiratory infections before follow-up	11	7	8			0.009	−0.003
Nighttime bottle in supine position			10	6	6	−0.026	−0.001
Floor area per person at home			13	5	3	−0.008	−0.056
Viral respiratory infections and tonsillitis of sibling(s) during follow-up	2	9			5	0.123*	0.079†
Socioeconomic status	7		7			−0.030	−0.050
Pets	13			8		−0.093‡	−0.023
Allergy of parent(s)	14			12		−0.015	0.004
Breast-feeding		13	4			0.024	−0.015
Indoor humidification	9	10	12			0.088‡	0.087‡
Sex (boys had more AOM attacks)	10	12				0.015	0.076†
Allergy of child	12	5				0.081†	0.062
Respiratory infections of parent(s) during follow-up	6				8	0.093‡	0.053
Place of residence				7			
No. of siblings						0.085†	0.090‡
Positive otitis history of parent(s)						0.101‡	0.097‡

AOM — acute otitis media.
*$p<.001$.
†$p<.05$.
‡$p<.01$.

In addition to human suffering, recurrent otitis attacks with effusion inside the middle ear impair the child's hearing ability at an age that is critical for the acquisition of linguistic skills. Children who have had prolonged middle ear effusion have shown depressed scores on intelligence tests, impaired development of speech and language, and poor performance in school.[66] The preventive procedures for this common and harmful illness are by no means composed only of medical aspects. Social and health educational factors play a very important role, too. That is why we are trying to analyze the combined risk of acute otitis media with a multivariant forecasting model.

The present analysis comprised a cohort of 1,294 children followed from the age of 7 months to the age of 2 years. Relevant epidemiologic data were collected during their regular checkup visits at child health-care centers, and their ears were examined and disorders were treated in specific study clinics.

A forecasting model for calculating the interrelative importance of given risk indicators was developed.[69] This mathematic method, ie, to find the best forecasting model in the Bayesian sense, follows the idea of stepwise multiple regression analysis, searches through all variables listed, and selects one by one the variable improving the model most, or at least affecting it with the fewest drawbacks if not improving it. The worth of the model is measured by the sum of false negatives and false positives. The minimum of this sum builds the optimum of the model. The variables in this list above this optimum affect the risk, with the rest of the variables being no longer useful in this forecasting model. In other words, the Bayesian approach reveals the variables containing any noticeable influence on the occurrence of acute otitis media. In our hands this model gave a correct classification in 65% to 71% of the cases; the higher the percentage, the higher the number of recurrent attacks per child.

Of the 22 variables studied, 12 to 15 were found to affect the combined risk of contracting one or more attacks of acute otitis media. The rank of importance of these 22 variables is shown in Table 8, indicating the interrelated power function of different variables in contracting acute otitis media.

The overwhelmingly highest risk indicator was day-care outside the study child's own home, regardless of how many recurrent attacks of acute otitis media were included in the analyses. However, this risk indicator became more important along with the increased number of recurrent attacks. Acute otitis media currently is preceded very often by upper respiratory tract infections,[70] and such infections tend to spread more easily the higher the population density. Day-care nurseries create a favorable environment for respiratory viruses to spread,[71] with acute

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otitis media as a sequela. Next in the risk indicator list came the number of attacks of acute otitis media among siblings, most probably because of increased exposure of a baby to infections brought in from outside the home; this was especially true with recurrent attacks. The same phenomenon can be seen with the type of housing, also.[73] The bigger the house with very many families living there, ie, apartment buildings, the higher the concentration of virus particles in the air inhaled by a baby.

Passive smoking is quite newly observed as a risk factor for acute otitis media, although there are contradictory reports on this point.[71-73] Our results showed that the mother's smoking seemed to increase most the risk to the baby of contracting acute otitis media and especially of contracting recurrent attacks. The number of smoking mothers in Finland is fortunately low, but on the other hand, because of this, information is sparse, and very definitive conclusions could not be drawn in this study. The protective effect of prolonged breast-feeding against respiratory infections is well known,[74] whereas data on its protective effect against acute otitis media are, however, now accumulating.[75] Our patients seemed to enjoy some protection against acute otitis media, but only during the first 12 months of life, ie, during breast-feeding time. Breast-feeding babies is becoming more fashionable again after a period of underrating this natural way of nourishment,[76] so future studies will reveal the optimal length of this "therapy."

In conclusion, this study suggests that the best place for a small child during the first years of life is in his own house where the mother breast-feeds him and does not smoke.

CURRENT STATUS OF OTITIS MEDIA IN THE AMERICAN INDIAN POPULATION

JOSEPH L. STEWART, PHD

The opinions expressed in this paper are those of the author and do not necessarily reflect the views of the Indian Health Service, US Public Health Service.

Incidence and prevalence determinations for a given disease typically involve specific research designs for those purposes. In the Indian Health Service (IHS), where resources for research are lacking, it is usually necessary to make prevalence estimates inferentially from assessing hospital records. The data in this report are based upon the number of visits for acute and chronic otitis media, with individual patients unspecified, and analyses of actual patient counts.

Otitis media was first listed in the IHS as a reportable disease in 1962. It has been no lower than the second highest in annually reported visits since that time, even though a special program was begun in 1970 to provide for the remediation and control of otitis media in American Indian and Alaska Native communities throughout the United States.

Over the 15 years of the otitis media program's existence (Table 9), hospital visits for acute and chronic otitis media have increased by 44%. During the same time the patient population has increased by 49%. The ratio of first visits to revisits changed over the first 10 years. For acute otitis media, the first visit to revisit ratio has changed from 62% to 54% for the first visit only. For chronic otitis media, the ratio has been more constant, from 32% to 38% for the first visit only. These data indicate increased awareness for follow-up for acute otitis media and less concern for follow-up for chronic otitis media. These findings, and all others not otherwise referenced, are from internal reports compiled by the IHS (Table 9).

An observation of particular interest in Table 9 is the consistency in the number of diagnoses of acute versus chronic otitis media in spite of the absence of IHS-wide criteria for defining acute and chronic disease. In general, the diagnosis of the physician is tabulated as recorded. In his assessment of patient care records, Toubbeh[77] found that in Alaska, Montana, and southern Arizona there was a high consistency in the diagnoses of chronic disease based upon presence of perforation, duration of the episode, and time between episodes. In Alaska, where 26.9% of the diagnoses were termed chronic otitis media, 1.1% showed perforation; in Montana, 9.5% cases were diagnosed chronic, with 0.8% showing perforation; in southern Arizona, 10.1% were diagnosed chronic, with 0.4% showing perforation. The consistency in diagnoses over time in Table 9 is noteworthy considering the IHS physician turnover rate and the wide variety of medical backgrounds of those making the diagnoses.

Evaluation of hospital records over the years of the program's existence shows three variables — sex, age, and blood quantum — to be particularly significant in making inferences about the natural history of otitis media.

TABLE 9. NUMBER OF OUTPATIENT VISITS FOR ACUTE AND CHRONIC OTITIS MEDIA, FISCAL YEARS 1971 TO 1985

	Acute Otitis Media		*Chronic Otitis Media*		
Fiscal Year	*No. of Visits*	*%*	*No. of Visits*	*%*	*Total*
1985	135,941	72.7	51,126	27.3	187,067
1984	129,022	71.7	50,731	28.3	179,753
1983	120,330	70.7	49,851	29.3	170,181
1982	108,561	69.8	47,029	30.2	155,590
1981	97,415	65.6	51,121	34.4	148,536
1980	90,408	70.0	38,668	30.0	129,076
1979	87,965	71.2	35,539	28.8	123,504
1978	95,692	81.5	21,671	18.5	117,363
1977	83,787	80.2	20,651	19.8	104,438
1976	81,126	79.5	20,941	20.5	102,067
1975	76,889	77.5	22,364	22.5	99,253
1974	74,915	78.3	20,717	21.7	95,632
1973	80,508	79.0	21,382	21.0	101,890
1972	74,107	77.7	21,312	23.3	95,419
1971	60,486	73.6	21,723	26.4	82,209

From Program Statistics Branch, Indian Health Service, Public Health Service, Department of Health and Human Services, Rockville, Md.

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ABSTRACT. The distribution of tympanogram types among 872 seven-year-old children from a random population sample was related to 14 features of the home environment reported by parents in a questionnaire. Parental smoking was an important determinant of middle ear underpressure and effusion, and accounted for much of the associations observed with dampness, crowding and rented accommodation. Gas cooking was associated with a higher prevalence of effusion, but a lower prevalence of underpressure: this may deserve further study.

After adjustment for seasonal variation, tenure and household smokers, the weekly mean temperature in the bedrooms of 34 children with Type B tympanograms was 18.2°C compared to 17.9°C for 190 children with Type A tympanograms. The equivalent figures for bedroom relative humidity were 51.8 per cent and 52.7 per cent. It is unlikely that heating or ventilation of the home is an important determinant of middle ear effusion and underpressure in this age-group.

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Impedance tympanometry and the home environment in seven-year-old children

DAVID P. STRACHAN, M.Sc., M.R.C.P. (Edinburgh)

Abstract

The distribution of tympanogram types among 872 seven-year-old children from a random population sample was related to 14 features of the home environment reported by parents in a questionnaire. Parental smoking was an important determinant of middle ear underpressure and effusion, and accounted for much of the associations observed with dampness, crowding and rented accommodation. Gas cooking was associated with a higher prevalence of effusion, but a lower prevalence of underpressure: this may deserve further study.

After adjustment for seasonal variation, tenure and household smokers, the weekly mean temperature in the bedrooms of 34 children with Type B tympanograms was 18.2°C, compared to 17.9°C for 190 children with Type A tympanograms. The equivalent figures for bedroom relative humidity were 51.8 per cent and 52.7 per cent. It is unlikely that heating or ventilation of the home is an important determinant of middle ear effusion and underpressure in this age-group.

Introduction

Little is known about the aetiology of middle ear effusion (Black 1985a), although evidence is accumulating of a substantial risk from passive exposure to tobacco smoke (Kraemer *et al.*, 1983; Black, 1985b; Hinton and Buckley, 1988; Strachan *et al.*, 1989). Studies in pre-school children have reported upon the relationship between middle ear disease and conditions in day care centres (Iversen *et al.*, 1985) and in the home (Birch and Elbrond, 1987), but no similar information has been published for children of school age. Although the overall prevalence of middle ear effusion is lower in older children, persistent effusions present a considerable burden to hospital services, and rates of surgery for glue ear are greatest in the five–seven year age group (Black, 1984).

The relationship between indoor air quality and respiratory disease in children has been extensively investigated using symptoms and ventilatory function as outcome variables. Particular areas of concern are possible hazards from suspended particulates due to parental smoking or household fires, nitrogen dioxide derived from unvented gas or paraffin appliances, and aero-allergens, such as mould spores or faeces of house dust mites, both of which tend to be more prevalent in damp houses (Samet *et al.*, 1987, 1988).

Tympanometric abnormalities are highly sensitive to frequent or persistent upper respiratory infections (Tos *et al.* 1979), and may therefore be a useful indicator of more general respiratory effects due to indoor air pollution. This paper explores the relationship between tympanometric findings and the home environment among seven-year-old children participating in a survey of the effect of damp housing upon respiratory disease (Strachan, 1988; Strachan and Sanders, 1989).

Methods

Sample selection

All children in their third (P3) year at a random sample of one in three primary schools within the Edinburgh city boundary were chosen. These children were aged 6¾ to 7¾ years in September 1986.

In the last week of November 1986, a postal questionnaire was sent to their parents, enquiring about respiratory symptoms in the child and conditions in the home, and including a form of consent to the remainder of the study. Children absent at the time of the launch were given a questionnaire on their return, and parents who had not responded after ten days were contacted by letter or telephone to maximize the number of replies. The parents of 1095 children received a questionnaire and usable replies were obtained from 1012 (92 per cent).

Written consent to further tests was obtained for 941 children (86 per cent of the target sample). Twenty of these children left school before examination, and two of the smallest schools (accounting for a further 20 children) were used for pilot studies of the respiratory examination protocol. The number of children eligible for inclusion in the clinical survey was therefore 901 (82 per cent of the target sample), 892 (99 per cent) of whom were eventually examined.

Ethical approval was obtained from the Paediatric/Reproductive Medicine Ethics of Medical Research Sub-Committee of the Lothian Health Board and from the Research Committee of the Department of Education, Lothian Regional Council.

Accepted for publication: 7 September, 1989.

Impedance tympanometry

Children were tested at school by the author during the period January to June 1987. Middle ear pressure, compliance, and the relative gradient of the tympanometric curve were measured on both ears using a Microlab 'Earscan' configured for impedance measurements (Micro Audiometrics, Port Orange, Florida, USA). This uses a probe tone of 226 Hz at 85 dB and sweeps from +200 to −312 daPa at 100 daPa/sec. Subjects were asked to swallow a sip of water immediately prior to the measurement, to ensure that patent eustachian tubes would be ventilated. Tympanogram types were defined on the basis of the modified Jerger classification proposed and validated by Fiellau-Nikolasen (1983):

Type	MEP (daPa)	Gradient	Interpretation
A	+200 to −99.9	>10%	Normal tympanogram
C1	−100 to −199.9	>10%	Mild underpressure
C2	−200 to −312	>10%	Severe underpressure
B	No peak	<10%	Middle ear effusion

The tympanogram type from the more abnormal ear of each child was used in the analysis. This permitted the inclusion of 23 children with satisfactory results from only one ear.

Monitoring of bedroom temperature and relative humidity

During the period January to April 1987, an attempt was made to visit the homes of 377 children, comprising all those in eight schools, those in the top quintile of the estimated bedroom humidity distribution (as described in detail by Strachan and Sanders, 1989) and the remainder of the homes reported to be affected by dampness or mould growth.

In each home, the temperature and relative humidity of the child's bedroom were monitored for seven days by thermohygrograph (Casella Ltd, London, UK). This instrument measures temperature by bimetallic strip and humidity by changes in the length of a treated human hair, and both are charted on a slowly moving drum. The thermohygrographs were installed in a position between three and six feet high and out of direct sunlight. On completion of the recording, their calibration was checked by a spot measurement of wet and dry bulb temperature using an aspirated psychrometer. The relative humidity was calculated from the wet and dry bulb thermometer readings using standard formulae (British Standards Institution, 1965).

Thermohygrograph charts were digitized for computer analysis and mean weekly values for temperature and relative humidity were calculated. Measurements were taken in 330 homes, of which 307 were usable in this analysis (81 per cent of the target sample). Technical problems with the instruments, including interference by the child or their siblings, accounted for most of the unusable recordings.

Relative humidity is a function of both vapour pressure (which reflects absolute humidity) and temperature (which determines the saturation vapour pressure at which condensation will occur). The relationship between indoor relative humidity and outdoor conditions is complex, depending upon the respective temperatures and vapour pressures. Thus, in well-heated bedrooms relative humidity was lower in colder weather, reflecting the lower outdoor vapour pressure usually found during the winter. However, in poorly-heated bedrooms the relative humidity was higher during the winter, because it was determined by the indoor temperature which varied to a greater extent with external conditions. Weekly mean indoor temperature and relative humidity measurements were adjusted for external climatic variations, as described in detail elsewhere (Strachan and Sanders, 1989).

Statistical analysis

Preliminary analyses were performed using Statistical Analysis System (SAS Institute Inc. 1985). The effect of housing conditions upon the distribution of tympanogram types was determined for 14 characteristics of the home environment reported in the questionnaire: tenure, number of persons per room, number of smokers in the household, use of gas for cooking, use of a coal fire, bottled gas appliance, paraffin heater, wood stove, presence of damp patches on walls, patches of mould or fungus, and the following characteristics of the child's bedroom during the winter months: number of children sleeping in the room, heat at night, heat during the day, and window left open at night. Most of the findings were negative, and results are presented in full only for seven variables for which an aetiological role in upper respiratory disease has been suggested by other studies. Trends in prevalence of Type B tympanograms across 2 × k contingency tables were assessed by the χ^2 statistic proposed by Mantel (1963).

The effect of housing conditions was investigated further by multiple logistic regression analysis, using the GLIM statistical package (Baker and Nelder 1978). Middle ear effusion (Type B tympanogram) was treated as the outcome variable, and those with Type A or Type C tympanograms as the comparison group. Housing tenure, domestic crowding (more than one person per room), gas cooking and dampness were treated as dichotomous explanatory variables, and the number of smokers in the household was included as a factor with three levels: none, one, two or more.

Results

Tympanometric data for the more abnormal ear of 872 children (98 per cent of those tested) were available for analysis. Overall, there were 546 Type A, 149 Type C1, 95 Type C2 and 82 Type B tympanograms. Twenty-six of the 82 children with a flat tympanogram in one ear had a flat tympanogram in the other.

Table 1 shows the distribution of tympanogram type by housing conditions, as reported in the postal questionnaire. Missing questionnaire data slightly reduced the numbers available for analysis by each housing variable. Middle ear pressure was lower among children from rented or crowded homes and from families with two or more smokers. Domestic fuels, dampness and mould growth had small or inconsistent effects upon the prevalence of underpressure (Types B and C combined), although Type B tympanograms were more common in all the 'exposed' categories.

TABLE I
Prevalence (%) of middle ear effusion and underpressure in the more abnormal ear by reported housing conditions

		More negative middle ear pressure (daPa)			
		+100 to −100 (Type A)	−200 to −100 (Type C1)	−300 to −200 (Type C2)	Negative no peak (Type B)
Tenure	own	64.6 (396)	16.3 (100)	10.6 (65)	8.5 (52)
	rent	57.8 (147)	18.5 (47)	11.8 (30)	11.8 (30)
Persons per room	<1.0	64.2 (187)	15.5 (45)	12.7 (37)	7.6 (22)
	1–1.5	62.0 (268)	19.0 (82)	8.6 (37)	10.4 (45)
	1.5+	59.8 (65)	13.9 (15)	14.8 (16)	11.1 (12)
Smokers in household	0	63.9 (292)	17.3 (79)	10.7 (49)	8.1 (37)
	1	63.3 (169)	16.5 (44)	10.9 (29)	9.4 (25)
	2+	56.4 (79)	17.1 (24)	12.1 (17)	14.3 (20)
Gas cooker	no	60.5 (221)	21.1 (77)	11.0 (40)	7.4 (27)
	yes	64.1 (320)	14.2 (71)	10.6 (53)	11.0 (55)
Coal fire	no	63.1 (511)	16.9 (137)	10.6 (86)	9.4 (76)
	yes	59.3 (32)	16.7 (9)	13.0 (7)	11.1 (6)
Dampness on walls	no	62.9 (462)	17.7 (130)	10.8 (79)	8.6 (63)
	yes	60.0 (78)	13.8 (18)	12.3 (16)	13.8 (18)
Mould growth	no	62.7 (492)	17.4 (137)	11.0 (86)	8.9 (70)
	yes	62.0 (49)	13.9 (11)	11.4 (9)	12.7 (10)

Number of children in parentheses.

The most marked difference in the prevalence of Type B tympanograms was between homes without smokers and those in which two or more adults smoked cigarettes. Overall, the trend of increasing prevalence with increasing number of smokers in the household was significant ($\chi^2 = 4.15$, df=1, $p<0.05$). The difference between owned and rented homes ($\chi^2 = 1.95$, df=1, $p>0.10$) and the trend of increasing prevalence of flat tympanograms with increasing housing density ($\chi^2 = 1.77$, df=1, $p>0.10$) could readily have occurred by chance. The prevalence of effusion was somewhat greater in the homes with damp patches on the walls ($\chi^2 = 3.01$, df=1, $0.05<p<0.10$).

There was also an excess of effusions in the homes with gas cooking ($\chi^2 = 2.81$, $0.05<p<0.10$), although the prevalence of underpressure was lower in this group. The number of children exposed to other sources of nitrogen dioxide in the home was small, but in each group the prevalence of Type B tympanograms was higher than among unexposed children: 11.3 per cent (7/62) for those exposed to bottled gas stoves, and 18.2 per cent (4/22) for children in homes with paraffin heaters.

In contrast to the effect of passive smoke exposure on the prevalence of middle ear effusion, the prevalence of pain or discharge in the ear over the past year differed little between non-smoking homes (23.5 per cent), homes with one smoker (25.3 per cent) and homes with two or more smokers (24.4 per cent). The corresponding proportions of children reported to have had tonsils or adenoids removed were 11.6, 14 and 12.1 per cent respectively. The prevalences of recent ear trouble and tonsillectomy or adenoidectomy varied little with respect to housing tenure, the use of gas for cooking, or the presence of dampness in the home (Strachan, 1988).

The prevalence of parental smoking (particularly both parents smoking) was higher in rented or crowded homes, and in homes affected by dampness or mould growth. When adjusted by multiple logistic regression for the effects of housing tenure, domestic crowding, gas cooking and damp walls, the excess of Type B tympanograms among children from homes with one smoker in the household (compared to none) was negligible (odds ratio 1.04, 95 per cent confidence interval 0.56–1.78). The effect of two or more smokers remained substantial, although of borderline significance when compared to non-smoking households (odds ratio 1.80, 95 per cent CI 0.96–3.40). The odds ratio estimates for Type B tympanograms, independent of parental smoking and other factors, were 1.28 (0.73–2.21) for rented housing, 1.05 (0.70–1.57) for domestic crowding (more than one person per room) and 1.38 (0.73–2.59) for damp patches on walls. The association of gas cooking with middle ear effusion was not confounded to any great extent by these factors, the adjusted odds ratio for homes with gas cooking being 1.40 (0.90–2.18).

The effect of indoor air quality was explored in more detail among the 307 children with tympanometric data whose homes had been visited in the thermohygrograph survey. Table II shows the mean temperature and relative humidity, adjusted for climatic variation, in groups defined by tympanogram type. There was little overall heterogeneity, and no evidence of a significant trend in bedroom temperature or humidity with degree of tympanometric abnormality. Further adjustment for housing tenure and the number of smokers in the household made little difference to these results (Table II). The mean temperature or relative humidity in each group might be misleading if the relationship between indoor conditions and middle ear disease were U-shaped, rather than linear. However, inspection of the spread of readings within each tympanogram group did not suggest that tympanometric abnormalities were more or less common at each extreme of the temperature or relative humidity distributions.

Discussion

This study has confirmed the importance of parental smoking as a risk factor for middle ear effusion, as discussed in detail elsewhere (Strachan et al., 1989). Of the remaining factors studied, gas cooking emerged as the

TABLE II
Mean adjusted weekly mean bedroom temperature and relative humidity by tympanogram type

	Tympanogram types				F statistics*	
	A	C1	C2	B	ANOVA	trend
As measured						
Temperature (°C)	17.87	17.27	17.72	18.18	2.09	0.07
Relative humidity (%)	52.70	54.99	51.93	51.99	2.18	0.23
Adjusted for tenure and number of smokers:						
Temperature (°C)	17.88	17.32	17.76	18.19	1.95	0.20
Relative humidity (%)	52.73	54.95	51.90	51.84	2.19	0.25
Number of children	190	59	33	34		

*Tests for heterogeneity (ANOVA) have 3 and 303 df. All are $p>0.05$.
Tests for trend have 1 and 305 df. All are $p>0.10$.

one with the strongest independent relationship to middle ear effusion, although it was quite likely that this association could have occurred by chance. The excess of middle ear effusions among children with unvented gas or paraffin appliances in the home was consistent with a hazard due to nitrogen dioxide exposure, although the overall prevalence of middle ear underpressure was lower in the children from homes with gas cookers. Such a discrepancy suggests chance variation rather than a causal relationship. This is the first report upon the association between gas cooking and middle ear disease, but Black (1985b) described a significant excess of cases attending for glue ear surgery among children from homes with open gas fires or paraffin heaters, which was attributable to confounding by parental smoking and birthplace. The present results should be regarded as a stimulus to further studies, rather than conclusive evidence for or against an environmental health hazard. Such studies may need to be large, or to use direct measures of pollutant levels, since a simple dichotomy between gas and other cooking fuel is a relatively crude indicator of personal nitrogen dioxide exposure (Ogston *et al.*, 1985).

These results do not suggest that the temperature or humidity of the home environment is an important determinant of middle ear effusion in children of primary school age. However, because the study was based upon children attending school, the proportion of their time spent in the home was less than for younger children. Caution is required in extrapolating these conclusions to other age-groups. Birch and Elbrond (1987) found that both minimal and copious ventilation through windows were associated with fewer Type B tympanograms in children aged 0–6 years but no direct measurements of indoor air conditions were obtained. **Their findings were based upon small numbers in each group and are difficult to interpret because copious ventilation was often associated with heavy smoking in the home.**

Both high and low ambient relative humidity have been proposed as factors promoting the spread of viral respiratory infections in droplet spray (Lester, 1948; Kingdom, 1960; Buckland and Tyrell, 1962). The lack of any relationship of tympanometric findings to ambient humidity in the child's bedroom does not suggest that domestic humidity is a significant factor in the transmission or infectivity of such infections. In this age-group, however, much of the transmission by droplet spray may be expected to occur at school.

Spot measures of relative humidity at the time of examination revealed much drier conditions in schools than in children's bedrooms, with relative humidity generally below 40 per cent. A review of controlled studies of humidification in working environments by Green (1984) suggested that the incidence of upper respiratory illnesses in adults is reduced if humidity is raised above this level, perhaps because drying and cracking of the nasal mucosa reduces host resistance. It is therefore possible that indoor atmospheric conditions at school were influential in determining the prevalence of middle ear effusion in these children, despite the lack of correlation between bedroom conditions and tympanometric findings. However, Iversen *et al.* (1985) found no relationship between middle ear effusion in younger children and the temperature, relative humidity or carbon dioxide concentration in their day centre. A similar investigation among children of early primary school age would be useful. Indeed, all studies exploring the respiratory effects of indoor air quality might consider the objective and sensitive technique of impedance tympanometry for inclusion alongside more conventional disease outcomes.

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Address for correspondence:
Department of Clinical Epidemiology and Social Medicine,
St George's Hospital Medical School,
Cranmer Terrace,
London SW17 0RE.

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Daigler, G.E., Markello, S.J., and Cummings, K.M., "The Effect of Indoor Air Pollutants on Otitis Media and Asthma in Children," Laryngoscope 101: 293-296, 1991.

In this case-control study, the authors investigated the possible relationship between home exposures to various indoor air substances and the incidence of acute otitis media and asthma in children. The authors reported that most of the "pollutant sources" assessed in the study were not associated with disease. For example, they reported that formaldehyde, renovations (a surrogate measure for dust exposure), and gas cooking (a surrogate measure of NO_2 exposure) were not significant predictors of disease in this study. The authors conclude that "this study confirm[s] the previously reported association between childhood asthma and exposure to pets and maternal smoking." Although the authors report that the study results suggest an association between otitis media and the use of woodburning stoves, they report that they were "unable to confirm the association between smoking and otitis" that has been "reported by others."

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The Effect of Indoor Air Pollutants on Otitis Media and Asthma in Children

Gerald E. Daigler, MD; Samuel J. Markello, PhD; K. Michael Cummings, PhD

This case-control study investigated the possible association between home environmental air pollutants and their effect on otitis media and asthma in children. Patients with physician-diagnosed otitis (n = 125, 74% response), with asthma (n = 137, 80% response), and controls (n = 237, 72% response) from a private pediatric practice seen between October 1986 and May 1987 were studied. A questionnaire inquired about housing characteristics (*i.e.*, age, insulation, heating system) and sources of indoor air pollution such as cigarette smoking, use of woodburning stoves, household pets, etc. Analysis of the responses confirmed previous findings of significant relationships between maternal smoking ($P = .021$), and the presence of pets ($P = .034$) and the occurrence of asthma. A newly reported relationship between exposure to woodburning stoves and the occurrence of otitis ($P < .05$) was reported. This implicates yet another risk factor (wood burning) in the etiology of otitis media.

INTRODUCTION

Over the last 20 years there has been increasing evidence implicating indoor air pollutants in either the etiology or perpetuation of respiratory disease in children.[1] Since the rise of heating costs in the early 1970s, numerous changes have occurred in the home building industry to conserve fuel. Energy efficiency and home insulation became priorities and little attention was paid to the effects of decreased air circulation and the entrapment and recirculation of indoor gases and particulate matter. At the same time, wood has become a more popular source of heat, especially in rural America.[2]

High concentrations of particulate matter occur as a result of indoor or outdoor wood combustion.[2–4] Woodburning stoves produce particulate matter that circulates along with measurable levels of formaldehyde and combustion by-products. Well-insulated homes (air tight) have been shown to have had as much as a ten-fold decrease in the air circulated per hour.[5–6] Recent findings of increased levels of naturally occurring radon gas in insulated homes attest to the fact that, in air-tight houses, particulate matter (radon) is concentrated rather than dispersed through air circulation.[5]

Several studies have reputed a positive association between levels of air pollutants and respiratory illness.[1,7] Sources of respirable contaminants include: urea formaldehyde, foam insulation, particle board, plywood, new furniture, carpeting, cosmetics, deodorants, and hair sprays. In addition, cigarette smoke, cooking oil, gas ranges (NO_2), wood stoves, and kerosene space heaters all contribute to indoor air pollution.[7,8] Mainstream or passive smoking (inhaled by the smoker) and sidestream smoke (from the burning cigarette itself) have been extensively implicated in the exacerbation of asthma and found to adversely affect pulmonary development and pulmonary function.[8] Numerous articles implicate exposure of children to environmental tobacco smoke as a cause of respiratory symptoms,[8] including adverse effects on middle ear effusions.[9–12]

The causal mechanism between pollutant exposure and manifestation of respiratory illness is complex. It is presumed that pollutants such as formaldehyde, NO_2, CO (the combustible by-products of cigarette smoke and wood burning) induce mucosal edema and increase mucous production and entrapment of the mucociliary apparatus to play a role in the disease process. To test the concept, a study was designed to investigate the relationship between exposure to indoor pollutant sources and the risk of presenting with otitis media or asthma in children. It was hypothesized that exposure to pollutants would be significantly greater among cases than controls, even after controlling for potential confounders.

METHODS AND MATERIALS

The study employed a case-control design. Both cases and controls were identified from a roster of patients seen in a private pediatric medical practice of four pediatricians located in Springville, NY, a rural community located 35 miles south of Buffalo, NY. Informed consent was obtained

From the Department of Pediatrics (G.E.D.), State University of New York at Buffalo, The Children's Hospital of Buffalo (G.E.D.), and the Department of Cancer Control and Epidemiology (S.J.M., K.M.C.), Roswell Park Memorial Institute, Buffalo.

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Send Reprint Requests to Gerald E. Daigler, MD, Division of General Pediatrics, The Children's Hospital of Buffalo, 219 Bryant St., Buffalo, NY 14222.

TABLE I.
Characteristics of Asthma Cases, Otitis Media Cases, and Controls.

	Asthma Cases (n = 137)	Otitis Cases (n = 125)	Controls (n = 246)
Age (years)	6.26†	4.10†	3.11
Mean (SD)	4.22	3.27	2.92
Age group (%)			
4+ years	63.8*	45.1†	22.7
2–3 years	14.7	18.6	30.2
<1 year	21.6	36.3	47.1
Sex (% male)	62.1*	60.2	48.4
Premature at birth (% yes)	18.1†	15.0	8.0
Breathing problems at birth (% yes)	12.9*	12.4*	4.9
Family history of otitis, sinusitis, asthma or allergies (% yes)	80.2*	73.5	68.9

*$P<.05$.
†$P<.01$.
Note: Distribution between each case group and controls tested by chi-square or one-way ANOVA.

in all cases. Both cases and controls were restricted to those who had been seen in the pediatric practice between October 1986 and May 1987. It was the intent to have cases represent children who were ill with a specific disease in a specific time period compared to a group of children not ill during the same period. Two case groups were identified for inclusion in this study: *1.* children with two or more office visits for separate episodes of otitis media and, 2. children hospitalized with a diagnosis of asthma, as well as others who had two or more office visits for asthma.

All diagnoses were made during the aforementioned time span and the diagnosis of acute otitis media was made by experienced attending pediatricians. Pneumatoscopy revealed an immobile tympanic membrane that appeared red, and was without normal architecture. Tympanometry was not done.

Controls were randomly selected from a group of patients seen for routine health maintenance, and who were without acute illness. They were seen in the office for well visits and did not present with an acute respiratory illness during the same period.

A questionnaire designed to assess exposure to air pollutants was mailed to the parents of cases and controls. The questionnaire inquired about the type of household (single family, apartment, mobile), the age of the house, heating system, type of heating fuel used, as well as the type of cooking stove. The use of an air purifier or central air conditioning, the cigarette smoking habits of household members, and the presence of household pets was also queried. In addition to the birth history, family history, and history of occurrence of illness, we asked about prematurity or breathing problems at birth, as well as family history of respiratory illness.

The initial questionnaire and one follow-up was mailed to the parents of children identified as participants in this study.

In the asthma group, 137 (80%) of 171 responded; in the otitis group 125 (74%) of 169 responded; and in the control group, 246 (72%) of 342 responded. A total of 508 (74.5%) of

TABLE II.
Household Characteristics and Exposures for Asthma Cases, Otitis Media Cases, and Controls.

Household Characteristics and Exposures	Asthma Cases (n = 137)	Otitis Cases (n = 125)	Controls (n = 246)
Age of current home (<10 Yrs)	22.4	27.9	17.0
Type of home:			
Single family	72.4	83.2	76.9
Mobile home	10.3	6.2	9.8
Home urea insulation	5.2	2.7	1.8
Formaldehyde products	24.1	31.0	34.7
New home siding during study period (% yes)	4.3	8.0	9.0
Woodburning stove (% yes)	29.3	42.5*	29.3
Kerosene heater	4.3	6.2	5.3
Electric baseboard heat	26.7	15.0	16.7
Fireplace (% yes)	25.9	23.4	20.0
Use humidifier (% yes)	53.4†	41.6	36.9
Use air purifier (% yes)	8.6	3.5	4.9
Gas cooking (% yes)	42.2	44.2	51.1
Mother smokes (% yes)	37.1	27.4	29.3
Father smokes (% yes)	23.5	26.5	30.2
Pets (% yes)	62.9*	60.2	51.5

*$P<.05$.
†$P<.01$.
Note: Distribution between each case group and controls tested by chi-square or one-way ANOVA.

682 participants responded to the questionnaire.

Analysis Methods

The distribution of subject characteristics and exposure indicators by group status was evaluated using chi-square or analysis of variance, as appropriate. To evaluate the effects of individual exposure indicators on disease status, while controlling for potential confounding factors, logistic regression analysis was used comparing each case group separately against control subjects.

A stepwise logistic regression analysis was conducted to evaluate the relationship between various home indoor exposures and otitis or asthma, while simultaneously controlling for selected covariates. Odds ratio (OR) and 95% confidence intervals (CI) were then computed.

RESULTS

The characteristics of study subjects are shown in Table I. Subjects with otitis media were more likely to be male, and report having been born prematurely or with breathing problems compared to controls ($P<.05$). Compared to control subjects, asthmatics were older (6 years *vs.* 3 years), more likely to be male ($P<.05$), to have been born prematurely ($P<.01$), or born with breathing problems or a family history of asthma, allergies, or otitis media ($P<.05$).

The environmental characteristics of subjects' houses are summarized in Table II. There were a few differences in potential sources of particulate matter found between case and control groups. The type and age of homes were not significantly different in cases and controls although living in a newer home (under

TABLE III.
Results of Stepwise Logistic Regression Analysis: Asthma Cases Versus Controls.

	β	SE	P	OR	95% CI
Covariates (Forced)					
Age GP A (age 4+)	1.9900	.3265	.001	7.31	(3.86, 13.87)
Sex (male)	.9127	.2852	.001	2.49	(1.42, 4.36)
Premature	1.0540	.4412	.017	2.87	(1.21, 6.81)
Breathing problem	1.2100	.4965	.015	3.35	(1.27, 8.87)
Family history	0.4416	.3244	.173	1.56	(0.82, 2.94)
Exposures Entered Stepwise					
Pet	.5965	.2807	.034	1.82	(1.05, 3.15)
Humidifier	.7959	.2772	.004	2.22	(1.29, 3.82)
Maternal smoking	.6716	.2918	.021	1.96	(1.10, 3.47)

β = logistic regression coefficient; SE = standard error of β; P = probability value; OR = odds ratio; 95% CI = 95% confidence interval.

10 years old) was an exposure variable (27.9% *vs.* 17% controls) and when later entered the stepwise model was marginally related to otitis ($P = .09$). Likewise, the use of electric heat, fireplaces, and gas cooking did not differ significantly. It was found that asthmatics were more likely to use humidifiers than the controls ($P < .01$). Significant ($P < .05$) was the increased incidence of having pets among the asthmatic cases, as well as the association of using wood stoves in the otitis case group ($P < .05$).

Multivariate Analysis

A series of stepwise logistic regression analyses were performed to evaluate the relationship between various indicators of indoor exposures and otitis or asthma, while simultaneously controlling for selected covariates. Covariates forced initially into each model included age (less than 2 years, 2 to 3 years, 4+ years), sex, premature status at birth (yes/no), and family history of ear infections, sinus infections, asthma, or allergies (yes/no to any). Exposure variables were permitted to enter the regression model in a stepwise fashion. Odds ratio (OR) and 95% confidence intervals (CI) were computed from regression coefficients and standard errors of variables generated in the final model.

As shown in Table III, after controlling for covariates, exposures found to be statistically significant predictors of asthma, were maternal smoking ($P = .021$) and the presence of pets ($P = .034$). Humidifier use was predominant in the asthmatic group ($P = .004$). Among covariates tested, being older (age 4+, $P = .001$), being male ($P = .001$), and having been born prematurely ($P = .017$) or with breathing problems ($P = .015$) were significantly associated with childhood asthma.

As shown in Table IV, study subjects living in homes with free-standing woodburning stoves were about 1.7 times ($P = .037$, 95% CI = 1.03, 2.89) more likely to present with otitis media than control subjects. Subsequent testing indicated that age of the house was not an effect modifier of the relationship between wood-stove use and otitis, but instead was an independent predictor. Two covariates were significantly related to otitis: being older (age 4+) and having experienced breathing problems at birth.

DISCUSSION

Findings from this study confirm the previously reported association between childhood asthma and exposure to pets and maternal smoking.[13,14] Study results suggest an association between the use of woodburning stoves and otitis media. This finding is consistent with Black's[15] report of increased middle ear effusion in subjects exposed to open fires and paraffin stoves. We were unable to confirm the association between smoking and otitis as shown by Kramer, *et al.*,[9] Iverson, *et al.*,[10] Richardson,[12] and Hinton and Buckley.[16] One explanation is that our study dealt with acute episodes of otitis media and the other studies addressed persistent middle ear effusions.

Honicky, *et al.* reported that moderate and severe symptoms in all categories of respiratory illnesses were more prevalent in subjects exposed to woodburning stoves relative to unexposed controls.[17,18] In these papers the question of otitis media was not specifically addressed. One possible reason wood stoves were more prevalent among the otitis group and not the asthmatics was that families with asthmatic children were counseled by the pediatric group to avoid using woodburning heat. Families of children with recurrent otitis had not received this same caution.

Most of the pollutant sources assessed in this study were not associated with disease. Neither formaldehyde exposure, renovations (a surrogate measure for dust exposure), or gas cooking (a surrogate measure for NO_2 exposure) were significant predictors of disease in this study. Each of these factors has been previously implicated as a potential source of indoor pollution, but their ability to potentiate disease has been reported as variable.[6,7] Few subjects in this study were exposed to foam insulation or kerosene heat, which made it difficult to assess these pollutant sources on disease risk. The small numbers of these exposure groups may reflect the fact that people are

TABLE IV.
Results of Stepwise Logistic Regression Analysis: Otitis Media Cases Versus Controls.

	β	SE	P	OR	95% CI
Covariates (Forced)					
Age GP A (age 4 +)	1.0090	.2889	.001	2.74	(1.56, 4.83)
Sex (male)	.4440	.2505	.076	1.56	(0.95, 2.55)
Premature	.4293	.4234	.311	1.54	(0.67, 3.52)
Breathing problem	.9632	.4812	.045	2.62	(1.02, 6.72)
Family history	−.0208	.2776	.940	0.98	(0.57, 1.69)
Exposures Entered Stepwise					
Woodburning Stove	.5471	.2617	.037	1.73	(1.03, 2.89)

β = logistic regression coefficient; SE = standard error of β; *P* = probability value; OR = odds ratio; 95% CI = 95% confidence interval.

aware of the hazards of these two entities and their use is diminishing. The use of humidifiers in the asthmatic group is consistent with physician advice to this group and probably not a predictor of disease.

Two indirect measures of "air tightness" were assessed in this study: age of the house and presence of new siding. At best, these measures represent a calculated guess as to "air tightness," under the supposition that new housing and/or siding reflects better insulation and reduced airflow. Study findings revealed a greater likelihood of living in a new home (under 10 years old) among both case groups relative to controls, but this was not statistically significant.

A limitation of this study was that exposure to indoor air pollutants in the home was assessed only indirectly through the use of a questionnaire. It is possible that among both cases and controls, some subjects were misclassified with regard to their "true" exposure status. Future studies should attempt to directly measure emissions to more accurately evaluate the impact of exposure on respiratory outcomes.

Another possible limitation were the criteria used to define case status. It is possible that the requirement of recurrent disease to identify eligible cases selected out a unique group of children with unusual susceptibility. Perhaps the effect of indoor pollutants would be more evident in those with only a single disease occurrence. Similarly, the control subjects in this study may have been unique in that they did not have a single occurrence of an acute respiratory illness during the time period studied.

In conclusion, we are at the point in our investigation to define, more accurately measure, and trace concentrations of indoor air contaminants, the measured effect that "air tightness" has on them, and their adverse effects on the respiratory health of children. It is important to know firsthand if measures used to conserve heat have led to increased levels of pollutants in the home, and subsequently diminished respiratory health among occupants. If so, then better means necessary to increase ventilation, circulation, and purification of air in households must be devised and installed to reduce the risk of such pollutant-induced disease. In particular, the significant relationship between otitis media and use of woodburning stoves is intriguing and warrants further investigation.

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Barr, G.S., and Coatesworth, A.P., "Passive Smoking and Otitis Media with Effusion," British Medical Journal 303: 1032-1033, 1991.

The authors performed a case-control study of 115 children aged 17 months to 11+ years who had otitis media with effusion confirmed by myringotomy and their matched healthy controls. The authors suggest that "exposure to cigarette smoke might induce instability of the mast cell walls and the onset of otitis media with effusion, but our data do not support this hypothesis." The authors state that cigarette smoking is more common in households of lower socioeconomic status but that "it is unlikely to be a risk factor for otitis media with effusion, although it may have an association."

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services combining medical and psychiatric expertise is needed.

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Passive smoking and otitis media with effusion

G S Barr, A P Coatesworth

Department of Otolaryngology, Queen Elizabeth Hospital, Birmingham B15 2TH

G S Barr, FRCS, senior registrar

A P Coatesworth, MB, senior house officer

Correspondence to: Mr G S Barr, Department of Otolaryngology, Walsgrave Hospital, Coventry CV2 2DX.

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Otitis media with effusion is reported to occur in over 80% of children at some stage, but surgery is indicated only when the condition is unresolved after three months. The main underlying causes of otitis media with effusion are eustachian tube malfunction, alteration of the mucociliary system, and nasopharyngeal disproportion. A family history of otitis media in parents or siblings and parental occupation and smoking may also be risk factors.[1] Hinton found a higher proportion of parents who smoked among 115 children undergoing surgery for otitis media with effusion than among 35 children attending an orthoptic clinic. A study of 892 7 year old schoolchildren in Edinburgh found an association between salivary cotinine concentrations from passive smoking and the presence of tympanometric abnormalities.[3] Such abnormalities, however, are not necessarily associated with otitis media with effusion.

Otitis media with effusion is diagnosed from the history and by otoscopy, audiometry, and tympanometry. No single entity is completely specific or sensitive and the condition is confirmed by myringotomy. We evaluated the relation between parental smoking habit and the presence of the established condition in a case-control study.

Subjects, methods, and results

In all, 115 children (70 boys, 45 girls; age range 17 months to 11 years 6 months, median 5 years 5 months) from the Cheltenham and Gloucester areas who had otitis media with effusion confirmed by myringotomy were matched according to age (within six months), sex, race, and social class to a control group of healthy children attending the ophthalmology and orthopaedic clinics. The children with otitis media with effusion had had hearing loss for at least three months and had been assessed by otoscopy, tympanometry, and audiometry. The control group had no history of ear problems and normal results on otoscopy and tympanometry with a portable Welch Allyn tympanometer.

The smoking habits of the parents of the children in the two groups were recorded after we had explained the aims of our study to them. Data were compared by McNemar's test for the presence of at least one adult in the household who smoked and whether the mother smoked. The differences between the number of cigarettes smoked by mothers and by all of the adults in the household were calculated by comparing the median values of paired data by the binomial method.

There were 230 adults in the study group and 228 adults in the control group. Seven patients were from socioeconomic class I, 14 from class II, 38 from class III, 43 from class IV, and 13 from class V. Parental smoking habits in the two groups were the same. There were no differences between the median number of cigarettes smoked in the two groups by mothers alone and by all adults in the household (95% confidence interval 0 to 0 cigarettes for both sets of data). The 95% confidence interval of the difference in proportion of mothers who smoked was −0·08 to 0·16 and that for all adults in the household −0·19 to 0·05 (McNemar's test; table).

Parental smoking habits among 115 matched pairs of healthy control children and children with otitis media with effusion

		No of pairs	
Group	Smokers present	Mother [illegible]	All adults in household
Otitis media	No	[illegible]	[illegible]
Control	No		
Otitis media	No	[illegible]	[illegible]
Control	Yes		
Otitis media	Yes	[illegible]	[illegible]
Control	No		
Otitis media	Yes	[illegible]	[illegible]
Control	Yes		
Total		[illegible]	[illegible]

Comment

Nasal symptoms, particularly those related to adenoid hypertrophy, are associated with the development of otitis media with effusion. Histamine concentrations in adenoid tissue are proportional to size, but ultrastructural evidence shows that the morphology of adenoid mast cells is the same in children with and without otitis media with effusion (A R Drake Lee, unpublished data). Exposure to cigarette smoke might induce instability of the mast cell walls and the onset of otitis media with effusion, but our data do not support this hypothesis.

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The prevalence of otitis media with effusion is highest where social conditions are poor,[1] and children of non-manual workers have significantly better hearing than do those of manual workers.[5] Cigarette smoking is commoner in those from the poorer socioeconomic classes but it is unlikely to be a risk factor for otitis media effusion, although it may have an association.

We thank Messrs G C Fox, M Hardingham, and J M Robinson for allowing us to study their patients.

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Menarche and reproduction after treatment for African Burkitt's lymphoma

Janet E Neequaye, Julianne Byrne, Paul H Levine

Burkitt's Tumor Project, Department of Child Health, University of Ghana Medical School, Accra, Ghana
Janet E Neequaye, MRCP, *associate professor of child health*

Epidemiology and Biostatistics Program, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA
Julianne Byrne, PHD, *senior staff fellow*
Paul H Levine, MD, *senior investigator*

Correspondence to: Dr J E Byrne, EPN 400, National Cancer Institute, NIH, Bethesda, MD 20892, USA.

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African Burkitt's lymphoma is a rapidly progressing cancer that responds quickly to cyclophosphamide. Since 1966 the Burkitt's Tumor Project in Accra has treated children with Burkitt's lymphoma chiefly by cyclophosphamide. A troublesome side effect after cyclophosphamide, however, is sterility. We sought to determine how chemotherapy might influence fertility in adults who had been treated for Burkitt's lymphoma as children.

Patients, methods, and results

Between 1984 and 1988 we attempted to interview and draw blood from every person treated at the University of Ghana Medical School for Burkitt's lymphoma between 1966 and 1988 who was at least 16 in 1988 and had survived at least five years from date of diagnosis. Because of difficulty in tracing boys results are given for girls only. Survivors were diagnosed at an average age of 9 years (range 3-17). All except three were prepubertal at diagnosis. All children were treated with cyclophosphamide and some also with other drugs. Cyclophosphamide was given fortnightly in boluses of 1400 mg/m² intravenously until remission, which was usually after three doses. The total dose ranged from 2·8 g/m² in two patients to roughly 9·0 g/m² in five (90-300 mg/kg).

Blood was sampled at the time of interview and date of the last menstrual period noted. Serum follicle stimulating hormone and luteinising hormone concentrations were measured by double antibody radioimmunoassay using the second international reference preparation as standard.

Most former patients lived in small rural villages with no access to postal or telephone systems. After excluding male patients and those who could not be located we interviewed 24 female survivors (two by proxy) and 13 sisters or neighbours as controls.

At follow up no survivor was still having treatment. All but two of the women were in good general health. One was blind and another had a chronic foot ulcer due to sensory deficit accompanying paraplegia. Both problems resulted from the tumour.

Survivors were similar to controls in age at interview, years of schooling, and sexual and marital experiences (table). Survivors, however, reached menarche significantly later than controls (age 13·5 v 12·2 years; $p<0·05$). This could not be attributed to treatment during puberty as the average age at menarche among the 16 survivors treated before age 11 was 13·3 years.

Of the 22 women trying for children, 21 had had at least one pregnancy. One woman who was treated for three weeks at age 11, reached the menarche at 16, and was 24 at follow up reported irregular periods and infertility for seven years. Sixteen of 17 married survivors had at least one child. Blood from 13 women was tested for follicle stimulating hormone and luteinising hormone concentrations. In none of these women were values abnormal.

Reproductive experiences of female survivors of African Burkitt's lymphoma and controls

	Survivors	Controls
Total No studied	24	13
No (%) with menstrual problems	1 (4)	0
No (%) ever had sexual intercourse	23 (96)	12 (92)
No (%) married	17 (71)	12 (92)
No (%) married with children	16/17 (94)	12/12 (100)
Average age at first live birth (years)	19·6	19·5
Average age at menarche (years)	13·5*	12·2*
Average age at marriage (years)	18·4	18·6

*$p<0·05$, t test

Comment

In this small study most female survivors of Burkitt's lymphoma seemed to be fertile. The single potential problem noted was the delay in menarche by more than one year. So far as we know this is the first such report after treatment with cyclophosphamide, which previously has been associated with dose dependent gonadal dysfunction.[1-3] The doses received in our study were just below that range.[2] To date the longest follow up of girls treated with cyclophosphamide (for the nephrotic syndrome) indicated normal fertility in 16 of 18 women in their mid-20s, but age at menarche was not studied.[4]

Follow up studies of survivors of cancer treated with various agents found changes in timing of menarche, some recording an earlier age at menarche, others a later age. Reasons for this effect are unclear. We also do not know what implication this would have for the timing of menopause.

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Rowe-Jones, J.M., and Brockbank, M.J., "Parental Smoking and Persistent Otitis Media with Effusion in Children," International Journal of Pediatric Otorhinolaryngology 24: 19-24, 1992.

The authors performed a case-control study on 163 children to determine whether a relationship may exist between otitis media with effusion requiring grommet insertion and parental smoking. The authors report that "analysis of findings in this study and previous reports has failed to demonstrate a significantly increased prevalence of smoking in at least one parent, amongst children with persistent otitis media with effusion requiring surgical intervention."

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Parental smoking and persistent otitis media with effusion in children

J.M. Rowe-Jones and M.J. Brockbank

Department of Otolaryngology, St. George's Hospital and Medical School, London (U.K.)

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Abstract

A total of 163 children were entered into a case-control study to determine whether any causal relationship exists between otitis media with effusion (OME) requiring grommet insertion and parental smoking. One hundred children with persistent OME formed the case group and 63 children with normal ears formed the control group. The prevalence of parental smoking in each group was then compared. Information was collected by questionnaire and further details about the subjects with regard to surgery of the upper respiratory tract were also gathered. Analysis of findings in this study and previous reports has failed to demonstrate a significantly increased prevalence of smoking in at least one parent, amongst children with persistent otitis media with effusion requiring surgical intervention.

Introduction

Otitis media with effusion is one of the most frequently encountered morbid conditions of childhood. It has a peak incidence between the ages of 3 and 6 years, occurring in 3.6% of 5-year-olds [17]. Up to 80% of all children may experience one episode by 5 years of age [14] with 5–10% requiring surgical intervention.

The condition is important because of its associated conductive hearing loss and consequent impairment of speech and educational progress [2]. It may also be a

Correspondence to: J.M. Rowe-Jones, Dept. of Otolaryngology, St. George's Hospital, Blackshaw Road, London SW17 0QT, U.K.

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precursor for chronic suppurative otitis media [11,12,14]. In those children requiring operation there are the further attendant risks of surgery and anaesthesia.

Many aetiological factors have been proposed for the development of OME [15]. Eustachian tube dysfunction is considered the final common pathway, contributed to by upper respiratory tract infection [8], local environment [9] and heredity [10].

Recent reports have implicated passive smoking as another predisposing factor in the pathogenesis of OME [3,4,13].

Materials and methods

Information was collected on 100 children at St. George's Hospital, all of whom had surgically proven otitis media with effusion at the time of grommet insertion. Our indication for tympanostomy tubes in this group was the presence of bilateral OME for more than 3 months.

Sixty-three paediatric in-patients attending for orthopaedic or general surgical operations formed a control group. None of these children had existing or previous middle ear pathology. All 163 subjects were referred from within the same Health District and so represent the same range of primary health care assessments before being considered for hospital referral.

Data was compiled on questionnaires. For each of the two groups the prevalence of parental smoking was determined and compared in a standard case-control study.

Subjects in the group with OME were also asked if they had had previous sets of grommets and this was then also related to parental smoking habits. A history of sibling tympanostomy tube insertion amongst this group of children was collected.

The study also examined the relationship of tonsillectomy and adenoidectomy to parental smoking amongst all 163 subjects. Tonsillectomy had been performed for recurrent tonsillitis. Adenoidectomy was performed in children with nasal obstruction, in the absence of nasal mucosal disease, and only after digital and visual examination of the postnasal space under anaesthetic confirmed hypertrophy. The children were therefore separated into new groups, namely operation-by procedure or non-operation. The prevalence of parental smoking in children requiring surgery to the adenoid or tonsil was then compared with that in children not requiring such surgery.

Results

All 163 children came from similar urban areas and social class. Fifty-three (53%) subjects in the OME group and 34 (54%) in the normal ears control group were male. Ages ranged from 2 to 12 (mean 6.01, S.D. 1.9) in the former group and 2 to 10 (mean 6.5, S.D. 2.5) in the latter.

Tonsillectomy and Adenoidectomy

The association of these procedures with parental smoking is demonstrated in Table II. No significant difference in the prevalence of parental smoking amongst the children who required tonsillectomy and the children not requiring this procedure, could be demonstrated (χ^2 with Yates' continuity correction = 0.7 df = 1. $P > 0.5$).

The 30 children undergoing adenoidectomy were also having grommets inserted for persistent OME. A greater proportion of children requiring adenoid removal had non-smoking as opposed to smoking parents.

Discussion

Passive smoking has already been implicated as causing an increase in respiratory illness during infancy and childhood [1,16]. Some authors have further suggested that OME is another direct hazard of parental smoking [3–5,13,15,18]. Studies demonstrating raised salivary cotinine levels in children proportional to their passive tobacco smoke exposure have been seen as complementing these findings [6,7].

It is argued that parental smoking might predispose to OME, not only by increasing upper respiratory tract infections but also by directly irritating the middle ear and eustachian tube mucosa and impairing mucociliary clearance. These actions may be augmented by antigenic substances in tobacco smoke stimulating the adenoid pad to release mediators of inflammation.

Our findings have failed to show any significantly increased prevalence of parental smoking amongst children with persistent OME, than amongst children with normal ears and no history of middle ear pathology. Correspondingly therefore, parental smoking does not result in a significantly increased risk of persistent OME in their offspring. In four previous studies on children in the general population [5,13,15,18] and two on children attending hospital [3,4], only that by Iversen et al. [5] found a significant association between middle ear effusion and passive smoking.

The groups we have studied were both drawn from an in-hospital population. In concentrating on patients requiring surgical intervention for OME, we have specifically looked for a relationship between effusions which are persistent, and parental smoking. It is possible that the prevalence of smoking amongst parents in the control group of children with normal ears may be higher than amongst children with normal ears generally, who do not require general surgical or orthopaedic treatment. However, this is likely to be a small difference only and given the high P values calculated would not produce any significant bias.

Our results were produced from a case-control study examining the prevalence of parental smoking amongst two groups of children. Data on smoking, whilst collected at one moment in time, must invariably be used to represent previous practice. However, none of the parents included had changed their smoking habit during the lifespan of their children at the time of questioning.

Hinton [3] studied children undergoing grommet insertion and compared them with a control group from an orthoptic clinic. He suggested there was a significantly higher than expected prevalence of smoking amongst the parents of children admitted for middle ear ventilation. Information was also collected on 26 children attending the ENT out-patient clinic. If the children from this clinic are also included for analysis, no significant relationship between surgical intervention for OME and passive smoking is demonstrated ($\chi^2 = 2.13$, $0.1 < P < 0.25$).

Strachan et al. [13] related salivary cotinine levels to the prevalence of middle ear effusions in primary school children. Only a third of the cases with flat tympanograms were statistically attributable to passive smoking. Unfortunately no conclusions about persistence of disease may be made from this prevalence study and the survey probably included only a few long standing cases. No information was given on the number of children awaiting grommets or with a previous history of grommet insertion.

In our study not only was no significant difference demonstrated between parental smoking amongst children with persistent OME and those with normal ears, but also a lower percentage of children requiring repeated sets of grommets had smokers as parents.

No significant increase in the prevalence of parental smoking was discovered in children undergoing tonsillectomy or adenoidectomy. Thus recurrent tonsillitis and symptomatic adenoid hypertrophy have not demonstrated any significant association with passive smoking. We have not then been able to support claims that parental tobacco smoke may contribute to offspring OME by causing adenoid hypertrophy.

Conclusion

There is no statistically significant difference in the prevalence of smoking in the parents of children suffering persistent otitis media with effusion, when compared to that amongst parents of children with normal ears.

Correspondingly therefore, parental smoking has not been shown to significantly increase the chance of children developing otitis media with effusion requiring subsequent tympanostomy tube insertion.

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[redacted]

Etzel, R.A., Pattishall, E.N., Haley, N.J., Fletcher, R.H., and Henderson, F.W., "Passive Smoking and Middle Ear Effusion Among Children in Day Care," Pediatrics 90(2): 228-232, 1992.

The authors conducted a study in an attempt to determine whether reported exposure to ETS was associated with an increased rate of otitis media with effusion or with an increased number of days with otitis media with effusion during the first three years of life. Children who had a serum cotinine concentration greater than 2.5 ng/mL were considered to have been exposed to ETS. Cases of otitis media with effusion were diagnosed using pneumatic otoscopy by nurse practitioners and pediatricians. The authors reported a relative risk of 1.38 [95% CI: 1.21-1.56] for the children with serum cotinine concentrations of 2.5 ng/mL. The authors conclude that "8% of the cases of otitis media with effusion in this population and 17.6% of the days with otitis media with effusion may be attributable to exposure to tobacco smoke."

Passive Smoking and Middle Ear Effusion Among Children in Day Care

Ruth A. Etzel, MD, PhD*‡; Edward N. Pattishall, MD, MPH‡;
Nancy J. Haley, PhD§; Robert H. Fletcher, MD, MSc*; and
Frederick W. Henderson, MD‡

ABSTRACT. One hundred thirty-two children who attended a research day-care center were studied to determine whether passive tobacco smoke exposure was associated with an increased rate of otitis media with effusion or with an increased number of days with otitis media with effusion during the first 3 years of life. Based on preliminary studies, a serum cotinine concentration of ≥2.5 ng/mL was considered indicative of exposure to tobacco smoke. Otitis media with effusion was diagnosed using pneumatic otoscopy by nurse practitioners and pediatricians who reviewed the children's health status each weekday. The 87 children with serum cotinine concentrations ≥2.5 ng/mL had a 38% higher rate of new episodes of otitis media with effusion during the first 3 years of life than the 45 children with lower or undetectable serum cotinine concentrations (incidence density ratio = 1.38, 95% confidence interval 1.21 to 1.56). The average duration of an episode of otitis media with effusion was 28 days in the children with elevated cotinine concentrations and 19 days in the children with lower cotinine concentrations ($P < .01$). It is estimated that 8% of the cases of otitis media with effusion in this population and 17.6% of the days with otitis media with effusion may be attributable to exposure to tobacco smoke. *Pediatrics* 1992;90:228–232; *otitis media, passive smoking, tobacco, day care.*

Numerous studies have shown that infants with smoking mothers have a greater risk of lower respiratory illness in the first year of life.[1-6] It is unclear, however, whether exposure to environmental tobacco smoke increases children's risk of upper respiratory illness including otitis media with effusion (OME).

An association has been reported between chronic middle ear effusion and tobacco smoke exposure. Two case-control studies[7,8] found that elementary school children who underwent tympanostomy tube placement were more likely to have lived in households where cigarettes were smoked. Neither study evaluated the relationship between passive smoking and frequency of OME or any measure of OME burden during the first 3 years of life. Also, in these studies, the estimate of a child's passive tobacco smoke exposure was based on parents' self-reports of their usual cigarette consumption. This may be an imprecise estimate, however, because the amount of tobacco smoke products actually absorbed by the child could vary considerably depending on the amount of smoke present in the environment, the child's proximity to the source of the smoke, and the room's ventilation characteristics. In the current study, a biochemical measure of exposure to tobacco smoke, serum cotinine concentration, was used.

The present study was designed to determine whether the children in a day-care center with elevated serum cotinine concentrations had more episodes of middle ear effusion in the first 3 years of life or more days with middle ear effusion than the children with absent or lower concentrations of cotinine in serum. Our a priori hypothesis was that children with serum cotinine concentrations ≥2.5 ng/mL would have an increased rate of OME in the first 3 years of life compared with children with serum cotinine concentrations <2.5 ng/mL.

METHODS

Study Setting

Children were selected from those enrolled in the day-care project of the Frank Porter Graham Child Development Center, a multidisciplinary research program.[9] Research on respiratory health has been an integral aspect of the day-care center's program since its inception in 1964, and general aspects of infection and illness documentation have been described previously.[10-12] Children were generally admitted to this day-care project as soon as possible after 6 weeks of age. They spent 8 hours a day, 5 days a week at the center and returned to their homes each evening. Smoking was not permitted in child-care areas of the center.

Study Design

We identified study children from among the 200 who had entered the center between 1964 and 1983. Children who were eligible for inclusion in this study met the following four criteria: (1) enrolled in the day-care center before 6 months of age, (2) remained at the day-care center for 18 months or more during the first 3 years of life, (3) spent no more than 4 consecutive months away from the day-care center during the first 3 years of life, and (4) had serum available for analysis. These eligibility criteria ensured that the children in the study were all under observation during the period of greatest risk for OME.[13]

One hundred thirty-two children met the eligibility criteria for this study. Of the 61 children who were ineligible, 27 entered after age 6 months, 30 were enrolled for less than 18 months prior to their third birthday, 4 were absent for more than 4 consecutive months, and 7 had no serum available for analysis because it had already been used for other purposes.

Detection and Diagnosis of Otitis Media With Effusion

Children's health status was reviewed each weekday by a full-time nurse on site at the day-care center; physical examinations were performed by pediatricians or nurse practitioners when any symptoms or signs of respiratory illness were present.

From the *Robert Wood Johnson Clinical Scholars Program and the ‡Department of Pediatrics, The University of North Carolina at Chapel Hill; and §American Health Foundation, Valhalla, NY.

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Middle ear effusion, the outcome of interest, was measured using pneumatic otoscopy. Clinicians made the diagnosis when the mobility of the tympanic membrane was markedly reduced or absent or when middle ear fluid was seen. Precise differentiation between purulent and nonpurulent effusions was not possible because tympanocenteses were not performed. An episode of OME was defined as a new effusion in one or both ears previously documented to have been free of fluid. All children in whom otitis media with effusion was diagnosed were treated with antibiotics by the nurse practitioners and pediatricians staffing the day-care center. Physical examinations were performed biweekly after diagnosis of middle ear effusion until the effusion had cleared. The shortest interval between two new onsets of OME was 2 weeks.

In this study, pneumatic otoscopy was not reinforced by tympanometry. Observer variability was controlled by limiting the number of clinicians who performed the examinations to two pediatricians and two nurse practitioners, all of whom were specially trained in pneumatic otoscopy.

Diagnosis of Respiratory Infection

Cultures of the upper respiratory tract for the detection of viruses and bacteria were obtained at the onset of each respiratory illness throughout the study period (1964 through 1983). Samples of respiratory secretions were obtained by performing a saline nasal wash and a throat swab. For this study, we were primarily interested in infection with three viruses (respiratory syncytial virus, adenoviruses, and influenza viruses) and colonization with two bacteria (*Haemophilus influenzae* and *Streptococcus pneumoniae*), because these had been demonstrated in a previous study[14] to be linked epidemiologically to the occurrence of OME. Viral infection (the percent of first illness cultures positive for adenoviruses, respiratory syncytial virus, or influenza viruses) and bacterial colonization (the percent of first illness cultures positive for *S pneumoniae* or *H influenzae*) rates were calculated for each child.

Measurement of Exposure

The measure of exposure to tobacco smoke was the child's serum cotinine concentration. Cotinine, the major metabolite of nicotine, is specific for tobacco exposure, is produced only in vivo, has a circulating half-life of 19 to 40 hours,[15,16] and can be measured by radioimmunoassay at very low concentrations.[16] In a previous study of a subset of these children, the serum cotinine concentration was significantly associated with a history of smoking in the home.[17]

As part of ongoing studies of respiratory diseases, each of the children enrolled in the day-care center had venous blood drawn in the spring and again in the fall of each year and placed in storage at −20°C. To determine each child's exposure to tobacco smoke, the serum sample drawn nearest the child's first birthday was thawed, an aliquot removed, and the sample shipped to the American Health Foundation in Valhalla, NY, where a radioimmunoassay for cotinine was performed without knowledge of the child's exposure status or illness history.[18]

On the basis of these serum cotinine concentrations, the 132 children were separated into two groups. Receiver operator characteristic curve analysis[19] of data obtained from our previous studies[17,20] had determined that a cutoff point of 2.5 ng/mL would minimize the sum of the false-negative and false-positive test results when using the serum cotinine to differentiate the children living in homes with at least one smoker from those who were living in homes where no one smoked. Therefore, those children with serum cotinine concentrations ≥2.5 ng/mL were classified as "exposed," and those with serum cotinine concentrations less than 2.5 ng/mL were classified as "unexposed" to tobacco smoke.

Measurement of Extraneous Variables

Each child's medical record was reviewed to obtain information on potential confounding variables including prematurity, congenital anomalies, breast-feeding (defined as one or more days of breast-feeding), socioeconomic status (as measured by the Hollingshead index),[21] atopic family history (as measured by parental report at admission examination of asthma or hay fever in immediate family), and history of OME prior to day-care center enrollment.

Statistical Tests

During the time OME is present, a child is not at risk of developing OME. For that reason, the incidence density was used to measure the frequency of OME. The incidence density of OME was calculated by dividing the total number of new cases of OME during the period of observation by the total number of child-days at risk during that period.[22] This denominator was calculated by subtracting from each child's total time under observation the number of days with OME. To test the null hypothesis that there was no association between exposure to tobacco smoke and the incidence density of OME, a large sample χ^2 test was constructed by using the normal approximation to the binomial distribution.[23] We used the test-based confidence interval suggested by Miettinen[22] to calculate the confidence intervals around the point estimate of the incidence density ratio. To test the overall association, stratified by potential confounding variables, the Mantel-Haenszel test statistic for density follow-up studies was used.[22] A one-tailed Kolmogorov-Smirnov two-sample test was used to test whether the distributions of otitis media incidence or prevalence rates were higher in the exposed than in the unexposed children.[24] Linear regression analysis was performed to identify significant predictors of the duration of otitis media.

RESULTS

The 132 children in this study included 71 boys and 61 girls; there were 100 blacks, 30 whites, and 2 children of mixed race. During the first 3 years of life, these 132 children were enrolled in the Frank Porter Graham Child Development Center for an average of 984 days (range 568 to 1075 days). The total length of time the children in the exposed and unexposed groups were enrolled in the day-care center between entry and age 3 was not significantly different (1001 days vs 976 days in the exposed and unexposed groups, respectively, $P = .15$). However, their child-days at risk differed significantly (752 vs 845 in the exposed and unexposed groups, respectively, $P = .01$).

Seventy-eight (59%) of the 132 children had detectable cotinine in their blood. The age at which the blood was drawn ranged between 4 months and 6.5 years with a mean age of 1.4 years. The cutoff point of 2.5 ng/mL resulted in the classification of 45 children as exposed and 87 children as unexposed to tobacco smoke.

Blood samples were obtained during the colder months (September through February) from 24 exposed children (53%) and 58 unexposed children (67%). Blood samples were obtained during the warmer months (April through August) from 21 exposed children (47%) and 29 unexposed children (33%).

Occurrence of Otitis Media With Effusion

Overall, in both groups combined, study children had an average of 7.78 (SD = 4.55) new episodes of OME per child in 984 days (2.9 episodes per year). Only one child (in the unexposed group) experienced no episode of OME in the first 3 years of life. The 45 exposed children experienced an average of 8.7 episodes of OME in the first 3 years of life, while the 87 unexposed children experienced 7.3 episodes in that period ($P = .08$).

Table 1 shows the incidence density of OME in the exposed and unexposed groups. The 45 exposed children experienced 393 episodes of otitis media in the first 3 years of life (incidence density = 0.0119/child-day), and the 87 unexposed children experienced 634

episodes in that period (incidence density = 0.0086/child-day). The resulting incidence density ratio was 1.38 (95% confidence interval 1.21 to 1.56). During the first year of life, the incidence density ratio for OME was 1.39 with a 95% confidence interval extending from 1.15 to 1.69 (Table 2).

The Figure illustrates the incidence density ratios and 95% confidence intervals for each of the first 3 years of life. Tobacco smoke exposure seemed to have its greatest effect in the first 2 years of life.

To examine further the differences in OME experience between exposed and unexposed children, a second, more conservative approach (a one-tailed Kolmogorov-Smirnov two-sample test) was used. This nonparametric test is used to test the hypothesis that two groups of observations have identical distributions. The distribution of otitis media attack rates in the exposed children was not significantly different than the distribution of otitis media attack rates in the unexposed children ($P > .05$).

Duration of Middle Ear Effusion

Consistent recording of OME duration data was initiated in 1968; 106 children had complete data on this variable. The 41 exposed children had a mean total duration of 268 days (an average of 28 days per effusion) while the 65 unexposed children had a mean total duration of 170 days (an average of 19 days per effusion) ($P < .01$). The distribution of total otitis media durations for the exposed children was significantly longer than that for the unexposed children ($P < .05$ by one-tailed Kolmogorov-Smirnov two-sample test).

Using linear regression analysis, we identified two significant predictors of the duration of middle ear effusion in this sample of 106 children: the child's cotinine concentration ($P = .0001$) and the age at which the child's first episode of OME occurred ($P = .03$). Those children with higher cotinine concentrations and earlier first episodes tended to have longer durations of middle ear effusion.

Because the highest frequency of middle ear effusion occurred in the 18 months between 6 and 24 months of age, and because all 132 children were enrolled during that time, subsequent analyses were restricted to this interval. Furthermore, because the discrepancy in duration of middle ear effusion could inflate the incidence density ratio, for all further analyses a standard duration of 7 days was subtracted for each episode of OME in children in both the exposed and unexposed groups.

Table 3 shows the incidence density of OME in the exposed and unexposed groups. The incidence density ratio is 1.24 with a 95% confidence interval extending from 1.07 to 1.43. This point estimate is slightly lower than that during the first year of life (1.39) and the second year of life (1.62) because of the different way in which the denominator was calculated. The point estimate of 1.24 is almost certainly an underestimate because of the use of the standard duration.

Potential Confounding Variables

Analyses were performed after stratifying for each potential confounding variable.[25] Mantel-Haenszel test statistics and P values were computed for each stratum. The overall association between serum cotinine concentration and OME remained significant after controlling individually for each of these potential confounding variables: gender, race, viral infection rate, bacterial colonization rate, coryza rate, atopic disease, breast-feeding, kerosene heater use in home, woodstove use in home, diagnosing clinician, and documentation of tympanic membrane mobility. Be-

TABLE 1. Incidence Density for Otitis Media With Effusion During the First 3 Years of Life According to Tobacco Smoke Exposure

	Exposed (n = 45)	Unexposed (n = 87)	Total (n = 132)
New episodes of otitis media with effusion	393	634	1 027
Child-days at risk	33 036	73 328	106 364
Incidence density	0.0119	0.0086	0.0097

Incidence density in exposed/incidence density in unexposed = 1.38 (95% confidence interval 1.21 to 1.56). Incidence density in exposed − incidence density in unexposed = 0.003 (95% confidence interval 0.002 to 0.005).

TABLE 2. Incidence Density for Otitis Media With Effusion During the First Year of Life According to Tobacco Smoke Exposure

	Exposed (n = 45)	Unexposed (n = 87)	Total (n = 132)
New episodes of otitis media with effusion	168	279	447
Child-days at risk	8 877	20 535	29 412
Incidence density	0.0189	0.0136	0.015

Incidence density in exposed/incidence density in unexposed = 1.39 (95% confidence interval 1.15 to 1.69).

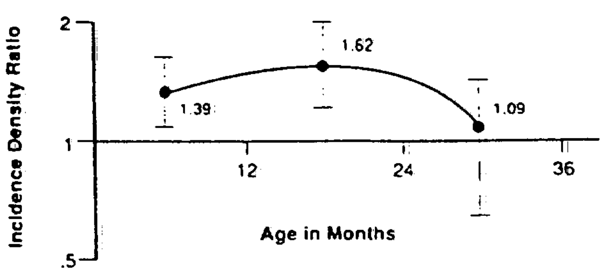

Figure. Incidence density ratios (logarithmic scale) and 95% confidence intervals for otitis media with effusion during each of the first 3 years of life.

TABLE 3. Incidence Density for Otitis Media With Effusion (Age 6 Months Through 24 Months) According to Tobacco Smoke Exposure

	Exposed (n = 45)	Unexposed (n = 87)	Total (n = 132)
New episodes of otitis media with effusion	318	504	822
Child-days at risk†	21 909	43 035	64 944
Incidence density	0.0145	0.0117	0.013

Incidence density in exposed/incidence density in unexposed = 1.24 (95% confidence interval 1.07 to 1.43). Incidence density in exposed − incidence density in unexposed = 0.003 (95% confidence interval 0.001 to 0.005).

† Standard duration of 7 days subtracted for each episode of otitis media with effusion.

cause only one child in the study group had tympanostomy tubes placed, this variable was not included among the potential confounding variables.

Population Attributable Fraction

The information in Table 3 can be used to calculate the fraction of OME cases in the population ("population attributable fraction") that might be preventable by eliminating children's tobacco smoke exposure. The risk difference of 0.003 is multiplied by the prevalence of smoking (which was about 38% in North Carolina at the end of this study) to derive the population attributable risk of 0.001. From the same table, the total rate of OME is seen to be 0.013. Hence the population attributable fraction is estimated to be 0.001/0.013 or 8%.

Likewise, we can estimate the number of days with otitis media which may have been preventable. An estimated 3565 days, or 17.6% of the total days with OME, may have been prevented if tobacco smoke exposure were eliminated.

DISCUSSION

The children in this study with elevated serum cotinine concentrations had a longer average duration of middle ear effusion than those with absent or lower serum cotinine concentrations. The difference in OME duration is especially notable insofar as the duration of illness may be a better measure of the burden of otitis media than the number of discrete episodes.

This study is unique with respect to both the measurement of exposure to tobacco smoke and the measurement of otitis media with effusion. The use of serum cotinine concentration, an objective measure of tobacco smoke exposure, may have avoided the potential misclassification inherent in parental reporting of smoking behavior. The prospective documentation of OME over the first 3 years of life at the Frank Porter Graham Child Development Center is also independent of the parental decision to bring the child to a clinician for a physical examination.

Our findings are consistent with the findings of Iversen et al,[26] who studied children between 0 and 7 years of age in Danish day-care centers and demonstrated an overall odds ratio of 1.6 (95% confidence interval from 1.00 to 2.5) for parental smoking and middle ear effusion as measured by tympanometry. That study reported point prevalence data in relation to parental reports of smoking behavior and estimated the overall fraction of middle ear effusion attributable to parental smoking to be 15%. Strachan et al[27] estimated that about one third of the cases of middle ear effusion in 6- to 7-year-old schoolchildren were attributable to passive smoking. The current study, using incidence density data, estimates the attributable fraction to be 8% in preschool children in day care.

When interpreting these results, it should be noted that because the children in this day-care center were in a smoke-free environment for 8 hours each day, our estimate of the difference in OME risk related to tobacco smoke exposure is likely to be an underestimate of the risk in the home setting. Had we compared children being cared for at home by smoking parents to those living in smoke-free homes, we might have demonstrated an even larger risk difference.

It is important to note that the use of the incidence density ratio does not take into account the fact that episodes of otitis media experienced by an individual child are not independent of one another. A more conservative test, the Kolmogorov-Smirnov test, did not verify that the difference between the distributions of attack rates in exposed and unexposed children was significant. In view of these conflicting results, we believe that any difference in the number of episodes of otitis media with effusion is probably small. However, the Kolmogorov-Smirnov test provided additional evidence that the difference in duration of otitis media between the exposed and unexposed children was significant.

The possibility of misclassification bias must be addressed. Since the pediatricians and nurse practitioners who diagnosed and treated each episode of otitis media were unaware of the study hypothesis, it is very unlikely that diagnosis of OME would have differed according to the exposure status of the child. Also, there had been no literature suggesting an association between tobacco smoke exposure and middle ear disease until 1983,[7] and data collection took place between 1964 and 1984. Furthermore, even if the clinicians had been aware of that potential association, they were unaware of the child's exposure status unless they were familiar with the child's parents' smoking habits. Although misclassification of exposure may have occurred on the basis of a single cotinine determination, it is very unlikely to have differed according to the disease history of the child. Our estimates of duration of OME were based on biweekly examinations of the study children after diagnosis. Although this is a somewhat imprecise measure, it is not likely to have differed according to the exposure status of the child. All of these possible sources of misclassification would have made it less likely that this study would demonstrate a difference between the exposed and unexposed groups, thus serving to strengthen these results.

Other researchers have documented that children in day-care settings have an increased incidence of otitis media.[28-32] This study was not designed to address that issue. Our results do demonstrate a higher incidence of otitis media than was reported by Teele and his colleagues.[33] They followed 2565 children for the first 3 years of life and found that one third of them had three or more episodes of otitis media, while 29% never had any otitis media in the first 3 years of life. Thus it is doubtful that generalizations can be made from our results to children who are not attending day-care centers. Our study site was chosen for convenience; population-based studies are needed to define further this apparent association.

There are several possible mechanisms by which tobacco smoke might influence the occurrence of middle ear effusion. Experimental data show that smoke exposure can result in goblet cell hyperplasia and mucus hypersecretion in the respiratory tract,[34] possibly including the eustachian tube and middle ear. This might lead to functional obstruction of a child's eustachian tube, especially when the exposure

occurs during a symptomatic viral upper respiratory illness, which could result in OME. Another possible mechanism is that tobacco smoke may diminish ciliary function. Some animal evidence indicates that short-term exposure to cigarette smoke causes ciliostasis and decreased mucociliary transport.[35] A third possible mechanism is that cigarette smoke and certain viral infections both alter the phagocytic antibacterial defenses of the respiratory tract, perhaps synergistically. This may lead to increased bacterial colonization and subsequently more otitis media.

Otitis media with effusion is an important public health problem. It is the most common illness diagnosed in US pediatricians' offices.[36] In 1980, otitis media accounted for 5 million office visits for children younger than age 3 in the United States.[37] It is estimated that $1 billion to $2 billion are spent on otitis media each year in the United States.[37] Since OME is such a common disease, prevention of even a small proportion of illness-days by limiting the exposure of children to environmental tobacco smoke could have a large public health impact.

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Maw, A.R., Parker, A.J., Lance, G.N., and Dilkes, M.G., "The Effect of Parental Smoking on Outcome After Treatment for Glue Ear in Children," Clin Otolaryngol 17: 411-414, 1992.

In this study, a sample of 201 children between the ages of 2-9 years with bilateral chronic otitis media with effusion were treated prospectively and at random by adenoidectomy, adenotonsillectomy, or with neither procedure. The parents of the children completed a questionnaire concerning their own smoking habits. The authors sought to examine the potential impact of parental smoking on the outcome of the treatment. The authors reported that "clearance of glue was statistically less frequent where the child's mother or where both parents smoked." The authors concluded that "the findings lend further support to professional and governmental opinions of a deleterious effect of passive smoke exposure on children and in this case parental smoking has been shown to have an adverse effect on the outcome of OME following surgical treatment."

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The effect of parental smoking on outcome after treatment for glue ear in children

A.RICHARD MAW,* A.J.PARKER,* G.N.LANCE† & M.G.DILKES*

*Department of Otolaryngology, Bristol Royal Infirmary and †Department of Computer Science, University of Bristol, UK

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The effect of parental smoking on outcome after treatment for glue ear in children

A sample of 201 children aged between 2 and 9 years with bilateral chronic otitis media with effusion (OME) were treated prospectively and at random by adenoidectomy, adenotonsillectomy, or with neither procedure. In all cases only a unilateral grommet was inserted and the contralateral unoperated ear was examined one year post-operatively for persistence or resolution of the effusion. A self-administered questionnaire was completed by the parents concerning their smoking habits. The resolution of effusion following surgery was assessed in relation to smoking by the mother and father separately and in combination. Clearance of glue was statistically less frequent where the child's mother or where both parents smoked. This was related to the number of cigarettes smoked by the mother or both parents. The adverse effect was demonstrable whether or not adenoidectomy or adenotonsillectomy had been performed for treatment. The findings lend further support to professional and governmental opinions of a deleterious effect of passive smoke exposure on children and in this case parental smoking has been shown to have an adverse effect on the outcome of OME following surgical treatment.

Keywords *otitis media with effusion passive smoking glue ear*

Although in general terms the smoking habit is slowly declining it is still said to remain the single most preventable cause of premature death and sickness. Thirty-one per cent of women and 35% of men were smokers in 1986 compared with 41% and 52% respectively in 1972.[1] Currently there is concern about the number of children who smoke and about the age at which the habit starts. Twenty-seven per cent of girls and 18% of boys are said to be regular smokers at the age of 15.[2] Smoking may affect an individual as part of an active process, but a significant number of children are affected by tobacco smoke in a passive manner, particularly in relation to maternal smoking. There is known to be a higher rate of minor ailments and absences from school in children whose mothers smoke.[3] A wide variety of studies have shown an adverse effect of parental smoking on the lower respiratory tract, with an increased incidence of pneumonia, bronchitis, asthma and coughs. Passive smoking also affects the upper respiratory tract and there is an increased incidence of sore throats which is especially related to maternal smoking.[4]

Correspondence: A.Richard Maw, Department of Otolaryngology, Bristol Royal Infirmary, Bristol BS2 8HW, UK

Studies in the past have shown conflicting results in relation to a causal link between passive smoking and the development of otitis media and middle ear effusions or glue ear. The relationship is complicated, firstly by the variable level of passive smoking to which the child is exposed, the age at which the studies are carried out and the other co-factors acting on the respiratory tract mucosa which are investigated coincidentally. Independently Kramer *et al.*,[5] Black,[6] Iverson *et al.*[7] and Hinton *et al.*[8] have shown an association between middle ear effusion and passive smoking exposure. They demonstrated a relationship with the degree of exposure and have also shown an increased risk with increasing age. However, no such relationship has been found by other investigators[9,10] and it has been suggested that this was because these studies were carried out in preschool children. Nevertheless, Stewart *et al.*[11] failed to show a causal relationship in children aged between 5 and 9 years

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An investigation of Dutch kindergarten children by Van Cauwenberge[12] also showed no increased risk of middle ear effusions in children of parents who smoke, but there was a tendency for the children to develop negative middle ear pressures as shown by tympanometry. The study by Kramer *et al.*[5] showed a clear relationship between the increased risk of middle ear effusion for children both in households where there were two or more smokers and also where there was a household consumption of more than 30 cigarettes a day, the risk increasing three and four-fold respectively. There was an additive effect when nasal congestion and atopy were taken into account, which elevated the risk to sixfold. Most recently, Strachan *et al.*[13] have confirmed a relationship between passive smoking and an increased level of salivary cotinine, a derivative of nicotine, in children in whom there are also tympanometric changes confirming negative middle ear pressure. They showed a relationship between these tympanometric findings with maternal smoking, the numbers of smokers in the house and the type of accommodation. This is further evidence of a causal relationship between exposure to cigarette smoke passively in children and changes within the middle ear which are demonstrated objectively by tympanometry. It is likely that some older children in a household will be active smokers but the habit is expected to be infrequent in children less than 9 years of age. The present study examines prospectively the effects of maternal and paternal smoking habits on the outcome of treatment for glue ear in children aged between 2 and 9 years. The surgical aspects of this study have previously been reported[14,15] and we now present the effects of passive smoking in children with glue ear on outcome of treatment 1 year following adenoidectomy and adenotonsillectomy. A similar group in whom no pharyngeal surgery was performed is also included, reflecting the effect of smoke exposure on the untreated condition.

Subjects and method

The study population consisted of 201 children aged between 25 and 103 months with a mean age of 63 months. There were 131 boys and 70 girls. Surgery was performed on a randomly allocated basis in 3 groups of which 81 had adenoidectomy alone, 47 adenotonsillectomy and 73 did not have surgery performed, either to tonsils or adenoids. (After 150 cases had been analysed and reported,[14] adenotonsillectomy was discontinued for ethical reasons and adenomectomy was performed at random.) Middle ear effusions had been confirmed on 3 occasions during a 3-month period preoperatively and at operation only a unilateral myringotomy and grommet insertion was performed. The contralateral unoperated ear was examined by a validated otoscopist to confirm the presence of an effusion.[16] Subsequent follow-up was made at 1 year ($\pm$3 months) later and the same observer examined the unoperated ear by pneumatic otoscopy to assess clearance or persistence of the effusion. Pure-tone or free field audiometry and impedance studies were also carried out pre and postoperatively as previously described.[15] A self-administered questionnaire was completed preoperatively by one or both parents with respect to their smoking habits. The occupation of the father was noted and classified into 6 social classes as follows:

(1) Professional
(2) Intermediate.
(3N) Skilled non-manual.
(3M) Skilled manual.
(5) Partly skilled.
(6) Unskilled.

Details were requested of the number of cigarettes (or tobacco equivalent for cigars and pipe tobacco) smoked per day during the previous 12 months by both the father and mother. They were also asked whether they had ever smoked during the previous 12 months. Parents were classified into non-smokers, mild smokers (1–9 cigarettes per day), moderate smokers (10–19 cigarettes per day) and heavy smokers (20 or more cigarettes per day).

STATISTICAL ANALYSIS

Bivariate statistics were used initially to investigate the distribution of the data which were shown in some cases not to be normally distributed. For this numerical data, a non-parametric Kruskal–Wallis analysis was used to compare the populations of those whose effusions had cleared against those in whom it remained in all the cases and in individual operation groups. For categorical data, such as those based upon no cigarettes, mild, moderate or heavy smoking as discussed earlier, a chi-squared analysis was used to make comparisons between the effusion resolved and effusion persisting populations, either as a whole or within each subgroup based on their treatment. The outcome variable of the presence or absence of glue in the unoperated ear at 1 year was assessed in relation to smoking by the mother and father, separately and in combination. The effects of smoking on outcome were therefore assessed for the whole group of 201 children and for the 3 treatment groups. An analysis of variance was also made to explore the relationship with the other variables, in particular the age and sex of the child, the type of operation performed and the socio-economic group of the father.

Results

The results of the statistical analysis are shown in Tables 1 and 2. There was significantly reduced otoscopic clearance of effusion in an unoperated ear at 1 year in those children whose parents smoked compared with those who did not

Table 1. Variables analysed in relation to otoscopic clearance in an unoperated ear at 1 year in all cases and with respect to treatment group

(1) Numerical data
- (i) Age
- (ii) No. of cigarettes or equivalent smoked by father per day
- (iii) No. of cigarettes or equivalent smoked by mother per day
- (iv) No. of cigarettes or equivalent smoked by mother and father per day

(2) Categorical data
- (i) Socioeconomic group
- (ii) Whether father had ever smoked during the previous 12 months (0 to 1)
- (iii) Whether mother had ever smoked during the previous 12 months (0 or 1)

(3) Derived variants
- (i) No. of cigarettes or equivalent smoked by father per day expressed as
  - 0 = 0 (none)
  - 1 = 1–9 (mild)
  - 2 = 10–19 (moderate)
  - 3 = 20– (heavy)
- (ii) No. of cigarettes or equivalent smoked by mother per day expressed as
  - 0 = 0 (none)
  - 1 = 1–9 (mild)
  - 2 = 10–19 (moderate)
  - 3 = 20– (heavy)
- (iii) BS1 0 = neither father or mother smoked
  - 1 = either father or mother smoked
  - 2 = both parents smoked
- (iv) BS2 sum of derived variants (i) and (ii)

This was evident in all cases where both parents or mother smoked, irrespective of whether surgery to the tonsils or adenoids was performed. Clearance was significantly enhanced in those who underwent adenoidectomy or adenotonsillectomy compared with those who did not receive pharyngeal surgery. The socioeconomic group of the father was, unexpectedly, found not to have a significant relationship to outcome by the analysis in terms of any of the smoking or other variables.

Discussion

This study shows for the first time an adverse effect on the outcome of surgical treatment for children with glue ear in relation to parental smoking habits. It further supports previous evidence in favour of a relationship between passive smoking and glue ear in children.[5-8] Bearing in mind the age of the children in this study it is unlikely that many were regular active smokers. These children had very well established bilateral disease. On average there was a previous history of subjective hearing loss for at least 18 months prior to inclusion in the study. The outcome variable, 'otoscopic clearance of effusion in an unoperated ear' was assessed by a validated observer[16] and we have reported previously the corresponding audiometric and tympanometric findings.[17] Despite the severity of the disease in these children we have shown that resolution of glue ear after treatment is reduced if the child's mother smokes and there is also a relationship between outcome and the number of cigarettes smoked by the mother. Furthermore, there is a more significant adverse effect on outcome if both parents smoke and again this

Table 2. Significant variables in relation to otoscopic clearance in an unoperated ear at 1 year

Parameters tested for significance between populations where fluid resolved and where it persisted	All cases ($n = 201$)	TA ($n = 47$)	A ($n = 81$)	No pharyngeal surgery ($n = 73$)
Numerical data: Kruskal–Wallis analysis				
(i) Age	$P < 0.05$	n.s.	n.s.	$P < 0.025$
(ii) Mother and father: no. of cigarettes or equivalent smoked per day	$P < 0.025$	n.s.	n.s.	n.s.
(2) Analysis of variance				
(i) Age	n.s.	n.s.	n.s.	$P < 0.025$
(ii) Mother: no. of cigarettes or equivalent smoked per day	$P < 0.05$	$P < 0.05$	n.s.	n.s.
(3) Categorical data: chi-squared analysis Derived variants				
BS1 (see Table 1)	n.s.	n.s.	$P < 0.05$	n.s.
BS2 (see Table 1)	$P < 0.05$	$P < 0.05$	n.s.	n.s.

TA, Adenotonsillectomy, A, adenoidectomy, n.s., not significant ($P > 0.05$).

relates to the number of cigarettes smoked by both parents. This adverse effect on outcome is irrespective of whether or not surgical treatment is carried out. As demonstrated in previous studies the present analysis confirms a significant effect of the child's age on outcome following surgery for glue ear in that clearance is less common in the younger patients but the effects of parental smoking are independent of the age of the child. The study provides further support to professional and governmental advice that parental smoking is harmful to children. It suggests that the beneficial effect of surgery for glue ear by adenoidectomy will be reduced if the child returns to a household where there is exposure to tobacco smoke.

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Lyons, R.A., "Passive Smoking and Hearing Loss in Infants," Ir Med J 85(3): 111-112, 1992.

This study investigated the possible relationship between exposure to ETS and hearing deficits and abnormalities of the eardrum in 87 10-month-old infants from a "socially deprived" area. The author reported that exposure to ETS was associated with 4.9 times the risk of hearing deficits and that approximately 75% of the cases of hearing loss were statistically attributable to ETS exposure. The author concluded that "the results of this study lend further weight to the hypothesis that exposure to cigarette smoke is a cause of hearing deficits in children."

hearing loss in 17 (81%). Seven infants were lost to follow up and the tympanic membranes were not satisfactorily visualised in three cases.

53% of infants came from single parent families and only 9.2% had a working parent: in all cases an unskilled labourer.

73% of mothers were current smokers and smoked on average 17.8 cigarettes per day. Overall 77% of infants were exposed to cigarette smoke. Surprisingly, there were no ex-smokers in the study group.

The mean (±SD) age of infants who attended was 10.67 (2.4) months and there was no difference in the age ($p=0.5$) or ($p=0.12$) sex distribution of those who passed or failed the hearing test. The main results are shown in the accompanying table. Infants who were exposed to cigarette smoke were nearly five times more likely to have a hearing deficit and were three times as likely to have visible abnormalities of the tympana. When infants with normal looking tympana who were not exposed to smoke were compared to those who were exposed and had abnormal tympana the prevalence of hearing deficits rose from 6.2% to 64.5% ($p=0.0001$).

Discussion

This is the first study to report an association between passive exposure to cigarette smoke and hearing loss in infants. Several studies have looked at this association in older children aged between one and 11 years with the majority in the two to seven year age range.[5,6,7,8,9,10,11,12,13] The three case control studies published report an odds ration of 1.6 - 2.8 of exposure to parental cigarette smoke in children attending hospital with middle ear effusions.[5,6,7] Six studies of children in the general population have reported on the association between middle ear effusions and exposure to passive cigarette smoke.[8,9,10,11,12,13] Only three of the studies could demonstrate a positive association.[8,10,13]

This study differs from the others in a number of respects. The main end point measured was hearing loss rather than abnormal tympanometric responses. Hearing was assessed blindly without knowledge of exposure status by a single operator thus eliminating inter observer bias. The specificity of diagnosis was high as 81% of diagnoses were confirmed by a medical audiologists. Indeed the specificity may be higher as glue ear tends to resolve spontaneously and this may occurred in some of the cases between testing and referral to the audiologist.[14] The study was confined to a single social class group in a small geographical area which would help to further reduce the possibility of bias.

The prevalence of hearing deficit in the non exposed group was 10% compared to 49% in the exposed group. If the association reported here is causal then 75% of hearing deficits in this cohort could be attributed to exposure to cigarette smoke. The results of this study support the hypothesis that passive exposure to cigarette smoke is a cause of middle ear effusion and hearing loss in children.

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Correspondence: Dr R Lyons, West Glamorgan Health Authority, 36 Orchard Street, Swansea SA1 5AQ, Wales.

Consultation liaison psychiatry within the general hospital: referral pattern and management

FREYNE A*, BUCKLEY P**, LARKIN C**, WALSH N***

*Central Mental Hospital, Dundrum, Dublin 14. **Cluain Mhuire Family Centre, Newtownpark Avenue, Blackrock, Co Dublin. ***Dept of Psychiatry, St Vincent's Hospital, Elm Park, Dublin 4

Abstract

The emergence of consultation psychiatry as an important psychiatric subspecialty is in part due to the siting of psychiatric units in general hospitals, the manifest advances in medical technology and the increasing elderly population needing specialist care. This paper describes an evaluation of all referrals to a liaison psychiatry unit in a 550 bed general hospital over a six month period. 205 requests for psychiatric consultation were received, which represented 2% of all admissions. There was considerable variation between departments with regard to the referral rate. Management most often consisted of advice, with over 50% of patients being subsequently referred for ongoing psychiatric care.

Introduction

Consultation liaison (CL) psychiatry has been defined as 'that area of clinical psychiatry which includes all diagnostic, therapeutic, teaching and research activities of psychiatrists in the non-psychiatric parts of the general hospital'.[1] The siting of psychiatric units in general hospitals and in the community (in line with current health policy[2]) and the advances in medical technology which result in new psychosocial and psychiatric problems for patients[3] will increasingly challenge the resources and expertise of the liaison psychiatrist.

Research in this area to date has mainly included the ascertainment of the prevalence of psychiatric 'cases' in samples of general hospital patients, and care provision in terms of cost effectiveness and of medical outcome.[4,5] One

children in the intravenous cannula group had to terminate their intravenous treatment prematurely because of complications and inability to maintain intravenous access. The silastic long line group had nearly 70% of their duration of treatment carried out at home compared to only 30% in intravenous cannula group (p value 0.014). The device life assessed was statistically highly significant in favour of the silastic long line group ($p<0.0001$). Cost of the device was higher in silastic long line group.

We came across only very few minor complications from silastic long lones. One child complained of pain after three days and the line had to be taken out and reinserted again in a different site. Four patients had leakage at the connector (blue) site which we corrected by simple manipulations. One line ruptured after administration of antibiotics using a large bore needle and a bigger syringe. No incidence of sepsis occurred with silastic long lines in our study.

Intravenous cannula complications are well known. Even though they were not very serious they warranted frequent change in cannulas. Pain, phlebitis, blockage and leakage into the tissues were very common problems. During the duration of treatment in the intravenous cannula group, finding suitable veins for cannulation became more and more difficult.

Discussion

It appears that silastic long lines are still only rarely used for antibiotic administration in cystic fibrosis patients in Ireland, even though their use is well established in many centres in the United Kingdom.[1] Since we have started using these lines in our cystic fibrosis population, the number of hospital admissions has been reduced. Children as well as parents were well disposed to the idea of silastic long line catheterisation because of the trauma these children have gone through due to repeat venepunctures before. The long line also allows greater freedom of mobility to the child. We allow them to take part in active sports, including swimming with the line in situ.

This device has given an opportunity to the cystic fibrosis children to spend their time with their parents at home while being treated actively. Even though the silastic long line group had a significantly higher device cost, reduced number of admissions and visits to the hospital reduce the overall cost of the treatment. It also decreases the workload of medical as well as nursing staff.

The skill and technique required for insertion of silastic long lines can be easily acquired by any house officer with suitable training. We have devised a simple management protocol regarding silatic long line care which is distributed to the parents and nursing staff. From our study we found that the silastic long line (Vigan) is an extremely useful device for intravenous administration in children with cystic fibrosis, which can be managed safely and easily at home.

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Correspondence: Dr JBG Watson, Dept of Paediatrics, Cork Regional Hospital, Cork

Passive smoking and hearing loss in infants

LYONS RA
Eastern Health Board, Rathdown Road, Dublin 7

Abstract

A cohort of infants scheduled to attend the 10 month developmental assessment were studied to determine whether hearing deficits are more common in those exposed to cigarette smoke. Hearing was assessed by the standard distraction test and those with persistent abnormalities were referred to a medical audiologist. Overall 77% of infants were exposed to cigarette smoke and 40% failed the initial hearing tests. Exposure to cigarette smoke was associated with a 4.9 times increase in the prevalence of hearing deficits and 75% of the cases of hearing loss were statistically attributable to exposure to cigarette smoke. The results of this study lend further weight to the hypothesis that exposure to cigarette smoke is a cause of hearing deficits in children.

Introduction

There is considerable evidence that passive exposure to cigarette smoke causes an increased frequency of bronchitis and pneumonia in the first year of life.[1,2] The aim of this study was to determine whether passive exposure to smoke is also associated with hearing deficits in infants, the majority of which are due to obstruction of the eustachian tube with consequent middle ear dysfunction.[3]

Subjects and methods

A cohort of infants due to attend their first scheduled developmental examination in a socially deprived area where chosen as the study group. As part of the examination hearing was assessed by the Stycar distraction test and the tympanic membranes inspected by a single trained operator.[4] The tympanic membranes were judged to be abnormal if there was scarring, retraction or visible inflammation. Subsequently a social occupational and smoking history was taken from the accompanying parent. Those who failed the initial hearing test were retested on two subsequent occasions three weeks apart and if the hearing was still abnormal were referred to a medical audiologist.

Categorical variables were analysed using the Mantel-Haenszal Chi Square test and continuous variable with the t-test.

Results

87 (83.6%) of 104 infants attended the scheduled examination. Thirty five infants (40.2%) failed the initial hearing test and 34 infants had visible abnormalities of the tympanic membranes. On repeat testing 21 infants persistently failed the hearing test and were referred to a medical audiologist who confirmed

Table - Results

	Exposure to smoke Yes	Exposure to smoke No	Relative risk	P value
Normal hearing	34	18		
Abnormal hearing	33	2	4.9	0.001
Normal tympana	34	16		
Abnormal tympana	31	3	3.0	0.01

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Rasmussen, F., "Protracted Secretory Otitis Media. The Impact of Familial Factors and Day-Care Center Attendance," International Journal of Pediatric Otorhinolaryngology 26: 29-37, 1993.

The authors of this study assessed the potential impact of various familial factors, day-care attendance and passive smoking on the incidence of protracted secretory otitis media (SOM) in a cohort of 1306 Swedish children followed from birth to age seven. The authors reported that children with siblings who had the same health problem were at four times the risk of SOM and children who attended a day-care center 12 or more months during the first four years of life had 2.6 times the risk of SOM. The authors reported that "no association was found between parents' smoking habits and the incidence of protracted SOM."

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Protracted secretory otitis media. The impact of familial factors and day-care center attendance

Finn Rasmussen

Department of Pediatrics, Uppsala University, Uppsala (Sweden)

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Key words: Secretory otitis media; Tympanostomy tubes; Incidence; Heredity; Day-care; Passive smoking

Abstract

This study's objective was to assess the impact of familial factors, day-care center attendance, and passive smoking on the incidence of protracted secretory otitis media (SOM). An unselected cohort of 1306 Swedish children were followed from birth to 7 years of age. Information about physician visits and insertions of tympanostomy tubes for SOM was collected at the ENT-departments in one Swedish county. The material was analyzed by life table methods and Cox's regression analysis. At the ages of 3, 5 and 7 years, 1%, 4% and 6%, respectively, of the children had been treated by tympanostomy tubes for SOM. The cumulative incidence of protracted SOM was four times higher among the children who had a sibling with the same health problem. Attendance at a day-care center of 12 or more months during the first 4 years of life increased the risk for protracted SOM by 2.6 times. No association was found between parents' smoking habits and the incidence of protracted SOM.

Introduction

Secretory otitis media (SOM) is a disease in which there is a middle ear effusion, the tympanic membrane is intact and symptoms of acute inflammation are absent. In this study protracted SOM is defined as SOM treated by insertion of a tympanostomy tube.

Correspondence to: Finn Rasmussen, M.D., Department of Pediatrics, University Hospital, S-751 85 Uppsala, Sweden.

A Danish study showed that 20% of 3-year old children had SOM at a screening tympanometric examination and 6% had SOM persisting for 6 months [6]. In another Danish study, also based on tympanometric measurements, SOM lasting for at least 3 months was found in 6% of 210 children (1–6 years of age) who did not utilize municipal day-care [1].

The etiology and pathogenesis of SOM is multifactorial and incompletely understood. Dysfunction of the Eustachian tube is important in the pathogenesis [11,13]. It has been suggested that heredity plays a part in determining a child's likelihood of developing SOM [10]. From tympanometric studies, day-care center attendance is a known risk factor for SOM [5,14,15]. However, previous research has not proven that enrollment in day-care centers comprises a risk factor for protracted SOM. Parental cigarette smoking has also been reported to be a risk factor for SOM by some authors [7,9,12], but not by others [3,16].

The research questions directing this population based cohort study are: (a) How large is the cumulative incidence of protracted SOM among Swedish preschool children? (b) Does the risk for protracted SOM increase if a sibling has or has had the same health problem? and (c) Are the type of day-care and parents' smoking habits risk factors for protracted SOM?

Methods

Study area

The municipality of Östhammar, with a population in 1980 of 21.028, is located in Uppsala county, 70 km (43 miles) northeast of the city of Uppsala and 140 km (87 miles) north of Stockholm. Two thirds of the population lives in five small urban centers and the remainder in rural areas.

Primary health care in Östhammar is available at one larger and three smaller primary health care centers. There was no otorhinolaryngologist (ENT-specialist) working in the study area from 1977 to 1988 and most specialized outpatient care and all inpatient care for children was provided at the two hospitals in Uppsala.

Subjects

The study population comprised all 1306 children born in the municipality of Östhammar between 1977 and 1981. Information about the children's date of birth, gender and address was collected from the County Civic Population Register. Additional demographic data, dates of possible emigration etc., were collected from parish offices in Östhammar. By the children's first, third and seventh birthdays 6%, 15% and 23%, respectively, had moved from the municipality of Östhammar.

Data on use of medical care

Information about all physician visits made by the 1306 children from 1 January 1977 to 31 December 1988 was collected from patient records held at the departments of otorhinolaryngology (ENT), audiology and phoniatrics at two

hospitals in Uppsala. All physician visits due to SOM were retro-actively recorded on a special form with information about the dates of visits and department. All patient records were scrutinized by the author. The principal outcome variable is date of insertion of a tympanostomy tube for SOM. An operation was recorded as tympanostomy for SOM only if middle ear effusion was reported by the ENT specialist. The ENT departments were the only places in Uppsala county where tympanostomy procedures were performed between 1977 and 1988.

Postal questionnaire

In 1990 all parents, including those who had moved from Östhammar, received a questionnaire by mail. Detailed questions were asked about family structure, number and age of siblings. form of day-care and parents' smoking habits during the child's first 7 years of life, the child's use of tympanostomy tubes, and the occurrence among siblings of SOM which led to insertion of tympanostomy tubes. This questionnaire was filled in and returned for 80% of the children.

Statistics

The starting point for all observation periods was the date of birth and the end point the date of a physician visit or an operation for SOM. The follow-up period was 7 years. Children who moved from the municipality or died before their seventh birthday are included in the analyses from the date of birth to the date of migration (or death). Children who moved (or died) before the studied event occurred are type-1 censored cases. Cumulative proportions of children with at least one ENT-physician visit for SOM or insertion of tubes for SOM at least once were estimated by the actuarial life table method [8]. The life tables and survivor functions in BMDP were used. Differences between survivor functions for sub-groups of individuals were compared by using Breslow's generalized test [2]. The effects of a set of covariates on the rate of physician visits for SOM, meaning the hazard rate, were analysed by Cox's proportional hazards regression model [4]. This model is appropriate for censored data if proportionality exists between hazard rates for different values of the covariates. The significance of associations between covariates and the hazard rate was tested by the likelihood ratio test [2,4]. The procedure for survival analysis with covariates in BMDP was used [2].

Reliability study

Recall bias in the parents' answers about their children's use of tympanostomy tubes was studied. The information from the cohort members' patient records about insertion of tympanostomy tubes for any reason during their first 7 years of life was compared to the equivalent data from the questionnaires.

Results

In the reliability study agreement was found for 99% of the children with respect to use or no use of tympanostomy tubes.

TABLE I

Secretory otitis media, insertion of tympanostomy tubes and chronic otitis media during the first 7 years of life

Diagnosis or type of operation	Diagnosis and/or operation during the children's first 7 years of life		
	No. of children ($n = 1306$)	Cumulative proportion	Mean age at diagnosis or operation (years)
First visit to an ENT specialist for secretory otitis media	101	0.10	3.9
Second visit to an ENT specialist for secretory otitis media	66	0.07	4.2
Tympanostomy tubes for the first time because of secretory otitis media	56	0.06	4.3
Tympanostomy tubes for the second time because of secretory otitis media	14	0.01	4.5
First visit to an ENT specialist for chronic otitis media	2	0.002	3.2

Ten percent of the children had visited an ENT-specialist at least once for SOM. Fifty-six (6%) were treated for SOM with a tympanostomy tube through one or both tympanic membranes at a mean age of 4.3 years (Table I).

TABLE II

Cumulative proportions of children treated with tympanostomy tubes at least once because of secretory otitis media during the first 7 years of life, by gender

Gender	Follow-up period in years of life							Proportion censored at the seventh birthday
	1.0	2.0	3.0	4.0	5.0	6.0	7.0	
Boys ($n = 633$)	0.00	0.00	0.01	0.01	0.03	0.03	0.04	0.24
Girls ($n = 673$)	0.00	0.00	0.01	0.02	0.04	0.06	0.07	0.22
Total ($n = 1306$)	0.00	0.00	0.01	0.02	0.04	0.05	0.06	0.23

TABLE III

Cumulative proportions of children treated with tympanostomy tubes because of secretory otitis media during the first 7 years of life, according to the presence of this disease among siblings

A sibling has or has had tympanostomy tubes	Follow-up time in years of life							Proportion censored at the seventh birthday
	1.0	2.0	2.5	3.0	4.0	5.0	7.0	
Yes ($n = 70$)	0.00	0.02	0.03	0.10	0.12	0.14	0.18	0.21
No ($n = 910$)	0.00	0.00	0.00	0.01	0.01	0.03	0.05	0.17

Table II shows that 4% of the boys and 7% of the girls had tympanostomy tubes inserted for SOM during the first 7 years. The difference was not statistically significant ($P = 0.10$).

Table III shows that SOM treated by tympanostomy tubes was at least three times as common among those children who had a sibling who had also received treatment for SOM by tympanostomy tubes ($P = 0.0000$). Only children who had at least one sibling are included.

Table IV shows proportions of children who got a tympanostomy tube through one or both tympanic membranes at least once during preschool age by type of day-care. Included are only those enrolled in either municipal day-care centers (DCCs) or in municipal family day-care homes (DCHs) for at least 12 months of

TABLE IV

Cumulative proportions of 710 children treated with tympanostomy tubes because of secretory otitis media during the first 7 years of life, by form of day-care

Form of day-care	Follow-up time in years of life							Proportion censored at the seventh birthday
	1.0	2.0	3.0	4.0	5.0	6.0	7.0	
Municipal day-care center ($n = 213$)	0.00	0.01	0.03	0.05	0.07	0.09	0.10	0.17
Municipal family day-care home ($n = 67$)	0.00	0.00	0.02	0.04	0.04	0.06	0.10	0.28
Day-care only in the child's own home ($n = 435$)	0.00	0.00	0.00	0.01	0.02	0.03	0.03	0.13

TABLE V

Cumulative proportions of 1 022 children treated with tympanostomy tubes because of secretory otitis media during the first 7 years of life, by mothers' smoking habits

The mothers' smoking habits	Follow-up time in years of life							Proportion censored at the seventh birthday
	1.0	2.0	3.0	4.0	5.0	6.0	7.0	
Non-smokers (n = 585)	0.00	0.00	0.01	0.02	0.04	0.05	0.06	0.17
10 cigarettes or more per day during the child's first 4 yrs of life (n = 247)	0.00	0.00	0.01	0.01	0.03	0.03	0.04	0.18
Mothers not belonging to any of the groups above (n = 190)	0.00	0.00	0.02	0.02	0.04	0.05	0.07	0.17

the first 4 years of life, and those cared for in their own homes during all of the first 4 years. Excluded are children who attended a DCC as well as a DCH during the first 4 years of life. The difference between the children attending a DCC and those cared for at home proved to be highly significant ($P = 0.0006$). The difference between children in DCH and those cared for in their own homes was on the other hand not significant ($P = 0.08$).

The children were divided into three groups according to their mothers' smoking habits: Mothers who smoked 10 or more cigarettes per day throughout their child's first 4 years of life, mothers who were non-smokers during the child's first 4 years, and the remaining group. No significant differences were found between any of these groups of children ($P = 0.23$) (Table V).

Analyses which included only the two-parent families were also performed. No difference was present in proportions treated with tympanostomy tubes between the children whose mothers and fathers were non-smokers, those whose mothers and fathers had smoked 10 or more cigarettes per day and children from the remaining two-parent families.

Table VI shows a multivariate analysis with three independent variables showing statistically significant associations with the dependent variable (occurrence of protracted SOM). Because of its importance for the totality one insignificant independent variable (enrollment in DCH) is also included in Table VI. This analysis included only children with siblings. The relative risk (RR) that a child would get tympanostomy tubes because of SOM increased 4 times if he or she had a sibling who had received treatment by tympanostomy tubes for the same reason.

TABLE VI

Cox's regression model for associations between independent variables and hazard rate for SOM treated with tympanostomy tubes (n = 975)

Independent variable	No. of children	Beta-estimate	Relative risk (RR)	95% confidence interval for relative risk
A sibling has or has had tympanostomy tubes				
Yes	70	1.42	4.15	(2.06; 8.38)
No *	905			
The child is oldest among the siblings				
Yes	433	0.58	1.79	(1.01; 3.18)
No *	542			
Municipal day-care center during 12 mos of the first 4 yrs of life				
Yes	197	0.95	2.59	(1.42; 4.74)
No *	778			
Municipal family day-care home during 12 mos of the first 4 yrs of life				
Yes	66	0.66	1.94	(0.68; 5.57)
No *	909			

* Reference category

The RR for protracted SOM was 1.8 times higher among those who were the oldest child in the family compared to the children who had older siblings. The RR for SOM treated by tubes increased 2.5 times for those children enrolled in a DCC for at least 12 months during the first four years of life, as compared to those who had been cared for in their own homes during their first 4 years. The RR for enrollment in DCH (1.94) was not statistically significant.

An analysis including the same variables as found in Table VI but only those cohort members whose siblings were born either before 1977 or after 1981 showed virtually the same results. In other analyses not shown no associations were found between the number of siblings and occurrence of SOM treated with tympanostomy tubes.

Discussion

It is an advantage that the children were as old as 9–13 years in 1990 when data about protracted SOM in siblings were collected. Very few of the cohort members

got new siblings after 1990 who might become new cases suffering from protracted SOM. Accordingly, it is highly likely that the information about protracted SOM in siblings is complete or almost complete.

As stated in Rockley and Rhys Evans [10], it is nearly impossible to determine whether or not an individual has suffered from SOM on the basis of otological history. However, the reliability of the information from questionnaires about a child's use of tympanostomy tubes was very high. Parents were thus fully capable of recalling their children's use of tympanostomy tubes during the previous 5–10 years.

The risk for protracted SOM increased four times if a sibling had had the same disease. When interpreting this finding it is important to keep in mind that the form of day-care and parents' smoking habits were taken into account in the multivariate analysis. Parents may still be more inclined to seek an ENT-specialist and perhaps suggest tympanostomy tubes for their child if previous experiences of that treatment of an older sibling had been positive. This type of confounding was eliminated by including place in sibship in the regression analysis. Since the form of day-care was controlled for, concordance between siblings cannot be explained by any tendency among siblings to attend the same type of day-care.

The RR for protracted SOM was 1.79 among those who were the oldest child in the family compared to the children who had older siblings. However, the lower limit of the 95% confidence interval for the RR was very near 1.00. Consequently this association might be due to random error.

In their case-control study, Rockley and Rhys Evans [10] examined otologically 146 parents of 73 children aged 1–4 years admitted to British ENT-departments for surgical treatment of SOM, and 70 parents of 35 children admitted to the same hospitals for surgery other than SOM. They described tympanic membrane abnormalities suggesting SOM previously in life among 39% of the parents of the cases with SOM and among 14% of parents of the controls. Based on this data the odds ratio of 3.84 is easily calculated. Regardless of differences in specific study design, there is close agreement between the odds ratio from Rockley's and Rhys Evans' study and the RR of 4.15 in the present study.

In accordance with Rockley and Rhys Evans [10], the present study clearly shows that familial factors are important in the etiology of protracted SOM. The intra-familial associations can not be explained by similarities among siblings with respect to form of day-care or passive smoking in the home. The pathophysiological mechanisms behind these intra-familial associations remain to be identified by future research.

Younger siblings of children with protracted SOM comprise a risk group for the same disease. While previous tympanometric studies have shown that enrollment in a DCC comprises a risk factor for single short episodes of SOM, the present study has confirmed attendance in DCCs as a risk factor for protracted SOM. Attendance in DCC is thus not suitable for children with protracted SOM. This form of day-care is even less appropriate if an older sibling to the child with protracted SOM has or has had the same disorder.

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